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THE FAILING RHEUMATIC HEART MECHANISMS AND PRESENT DAY THERAPY*

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"Contemporary history embarrasses a writer not only because he knows too much, but also because what he knows is too undigested, too unconnected, too atomic. It is only after close and prolonged reflection that we begin to see what was essential and what was important, to see why things happened as they did, and to write history instead of newspapers."

Speculum Mentis, or the Map of Knowledge
R C. Collingswood
Clarendon Press (Oxford) 1924

Cardiac disability in persons with rheumatic heart disease which ultimately leads to congestive heart failure is the end result of the interaction of many defects. These defects are myocardial, valvular, pulmonary and associated illnesses. Associated illnesses may contribute to or precipitate failure. They may be obvious or subtle. They are always important because they are frequently the immediate basis for sudden deterioration of cardiac function.

Each defect may be primary in the sense that it is independent of other defects, secondary to one or more of the others or both primary and secondary. Such a complex combination of causes of failure makes analysis of the contribution of each defect difficult and, with present knowledge, at times impossible. Such knowledge, however, is needed if one is to predict the overall cardiac effect of treatment that is specific for each defect.

Prophylaxis would be simpler for the physician and better for the patient. There is reason to hope that clinical disability due to rheumatic heart disease may become of historical interest. The severity of the rheumatic process has decreased over the past century. This change may be due to natural selection, decreased virulence of the rheumatic agent, improved socioeconomic conditions and to dietary factors, of which Coburn[3] believes that something in eggs is of particular importance. Penicillin has accelerated the decline in severity and perhaps has decreased the incidence of rheumatic heart disease.

*Based in part upon talks delivered at the Heart Association of Southeastern Pennsylvania, the American College of Chest Physicians, the Seton Hall Medical School Graduate Course and the George Washington University School of Medicine.

This change in incidence and severity is illustrated by the experience at St. Christopher's Hospital for Children during 1958 which has been summarized by Wells and Garfunkle[35]. This hospital receives patients from its staff and that of Temple University Hospital and other hospitals, from the neighborhood, from city schools and from city and state health centers.

TABLE 1.—CARDIAC PATIENTS AT ST. CHRISTOPHER'S HOSPITAL, 1958

New Clinic Patients	102
1) Congenital	45
2) Rheumatic	5
Hospital patients	322
1) Congenital	199 (43 deaths)
2) Rheumatic	50 (No deaths)
a) No heart disease	20
b) Heart disease	30 – Myocarditis 1
	MI 29 (2)*

With A.I. 5 (2)*, M.S. 3,2 ?

*Lost murmur before discharge from hospital

Table 1 shows that of 102 new cardiac clinic patients, only 5 were rheumatic. Of 322 children hospitalized for apparent heart disease, only 50 were rheumatic. Of these 50, twenty had no heart disease, one had myocarditis and 29 had the murmur of mitral insufficiency; 5 had, in addition, the murmur of aortic insufficiency and 3 that of mitral stenosis; 2 had a questionable murmur of mitral stenosis. The murmur of mitral insufficiency disappeared in 2 and that of aortic insufficiency in 2 others before discharge from the hospital. There were no deaths from rheumatic heart disease. This experience differs greatly from that of 25 years ago when there was insufficient room for all the rheumatic children who needed hospital care and when deaths from rheumatic fever in children were greater than those due to almost all other diseases taken together (Wilson[36]).

Specific prophylactic treatment for the prevention of rheumatic fever is accomplished primarily by treating promptly an infection due to the Group A hemolytic streptococcus with 1,200,000 units of benzathine penicillin G given intramuscularly. Two hundred thousand units of penicillin G or V should be given by mouth twice daily to all children and young adults who have had or are suspected of having had or, because of their family history, are potentially susceptible to rheumatic fever. This prophylactic treatment should at least be doubled for 2 days before and after an operation that may permit dissemination of streptococci.

Active rheumatic fever should be treated with the bactericidal dose of penicillin followed by the daily prophylactic dose for at least 5 years and until early adulthood is past. Convalescence should be started 2 weeks after clinical and laboratory signs of infection have subsided. Physical restrictions in the absence of symptoms are unnecessary. It is important to bear in mind that children and even adults may deny symptoms when engaging in competitive sports or gainful employment.

Corticosteriods should be used when carditis is present. The usual adult dose is 150 mg. of prednisone or its equivalent a day. Wilson and Linn[38] increase the dose if the eosinophil count is 10% or more than that of the preceding day. Most physicians use the clinical response to determine the dosage and do not hesitate if necessary to produce temporary mild Cushing's syndrome. Wilson and Linn terminate steroid therapy abruptly after 7 days but start a second course if clinical activity appears. Most physicians continue steroids for 4 weeks.

Steroid therapy frequently dissipates congestive failure. Salt restriction is indicated. Other conventional medical

treatment for congestive failure may be added if response to steroids is slow or poor or if relief is urgently needed. The average dose of digitalis should not be exceeded without frequent clinical and electrocardiographic search for digitalis toxicity.

Clinical evidence of carditis is frequently mild and short-lived. Microscopic evidence, on the other hand, persists for years. Furthermore, there is no difference in the microscopic appearance of those who have had from those who have not had clinically active rheumatic fever. Moreover, the microscopic findings in biopsies of the left atrial appendage contain the earliest forms of rheumatic lesions identical with those found in acute rheumatic carditis at necropsy. The disease therefore must be considered subclinical for part or all of its course. Acute rheumatic fever is only an episode or a series of episodes which tend to accelerate the underlying deterioration (Lannigan[15]).

Because the recurrence rate of acute rheumatic fever is low, about 2.5% per year in children and approximates zero after the age of 20, the initial rheumatic process tends to determine the subsequent course of events and the pattern is frequently firmly established at 20 years (Wilson and Linn[39]). Death before the age of 20 is rare. There were no deaths due to rheumatic heart disease in 1958 at St. Christopher's Hospital. Death from rheumatic heart disease during adolescence is also rare. Only one such patient was admitted into Temple University Hospital during the past decade. This Negress developed her first bout of active rheumatic fever at 8 years of age. For the succeeding 8 years she had been admitted repeatedly to the same children's hospital for apparent recurrent active rheumatic fever, aortic regurgitation and cardiac failure. At age 16 she was admitted by the police to Temple University Hospital. She was emaciated, orthopneic and edematous from the hips down. Her blood pressure was normal. The left hemithorax bulged forward. A right ventricular systolic lift was obvious as well as a left ventricular thrust in the posterior axillary line. Here, and over the xyphoid region, pansystolic murmurs were audible. A pandiastolic murmur was heard along the left border of the sternum. Atrial fibrillation was present. A diagnosis of rheumatic heart disease, marked enlargement of all cardiac chambers, mitral, tricuspid and pulmonary regurgitation, right ventricular hypertension, atrial fibrillation and congestive heart failure was made. This diagnosis was supported by the roentgenogram of the chest (Fig. 1) which showed cardiomegaly with enlargement of the pulmonary arteries and their major branches and also by the electrocardiogram which showed right ventricular hypertrophy and gigantic F waves.

Necropsy verified the presence of cardiac enlargement with a huge right atrium, right ventricle and left ventricle. The mitral, tricuspid and pulmonary rings were dilated but the leaflets and cusps were but minimally scarred and of apparent normal areas.

Dilatation of the valve rings in the absence of significant pathology of the leaflets, cusps or their supports can therefore produce regurgitation and has been previously emphasized by Coombs[5]. Regurgitation secondary to myocardial involvement is an important and frequent element even when the valves are severely affected by rheumatic fever. This statement should not be interpreted to mean that primary correction of mitral regurgitation is not indicated if mitral regurgitation solely or predominantly of myocardial origin is present. Indeed, mitral

regurgitation may be due to a ruptured chorda tendinea, an obviously surgical problem.

Fortunately, most rheumatic children have a milder degree of involvement and reach adulthood with but slight cardiac enlargement and mitral regurgitation. The mortality in this group, except for rare and unpredictable bacterial endocarditis, is not significantly different from the general population as a whole (Wilson and Linn[39]). They require no physical restrictions with the possible exception of competitive athletics and heavy physical labor. Indeed, the murmur itself may disappear in a significant number of persons.

This benign course indicates that mitral regurgitation does not usually beget mitral regurgitation. Even moderate mitral regurgitation after bacterial endocarditis or mitral valvotomy tends to become stabilized after the myocardium has adjusted to its new load. Considerable cardiac enlargement with mitral regurgitation may also remain stabilized for decades

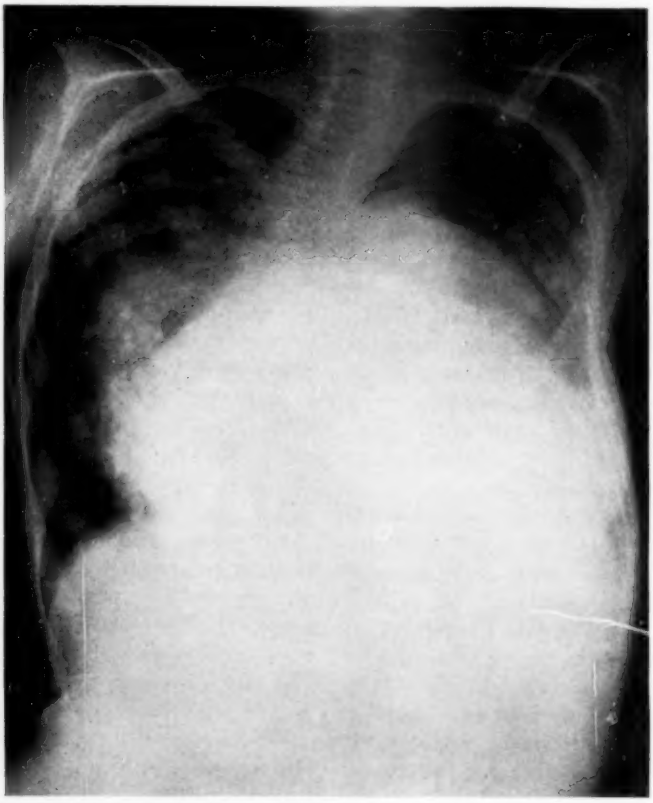

Fig. 1.—D.S., a 16-year-old girl. Note the huge heart, huge central pulmonary vessels and clear lung fields. The electrocardiogram shows atrial fibrillation, gigantic f waves and right ventricular hypertrophy. Necropsy disclosed a huge heart with enlargement of all chambers predominantly the right side and dilatation of the mitral pulmonary and tricuspid orifices. The mitral leaflets were minimally scarred and thickened but of almost normal area.

and fail because of myocardial dysfunction as illustrated in the following example:

M.M., a 50-year-old well known artist, was asymptomatic and had a stabilized cardiac silhouette (Fig. 2) with "pure" mitral regurgitation for at least 25 years. Three years previously he began to develop recurrent bouts of dyspnea and of atrial fibrillation which finally became permanent in 1958. He was digitalized and admitted for possible correction of his mitral regurgitation. Cardiac catheterization disclosed a normal cardiac output, normal right and left heart pressures and no diastolic atrioventricular gradient. He was discharged on a maintenance dose of digitalis and has remained asymptomatic until the time of writing, one year later.

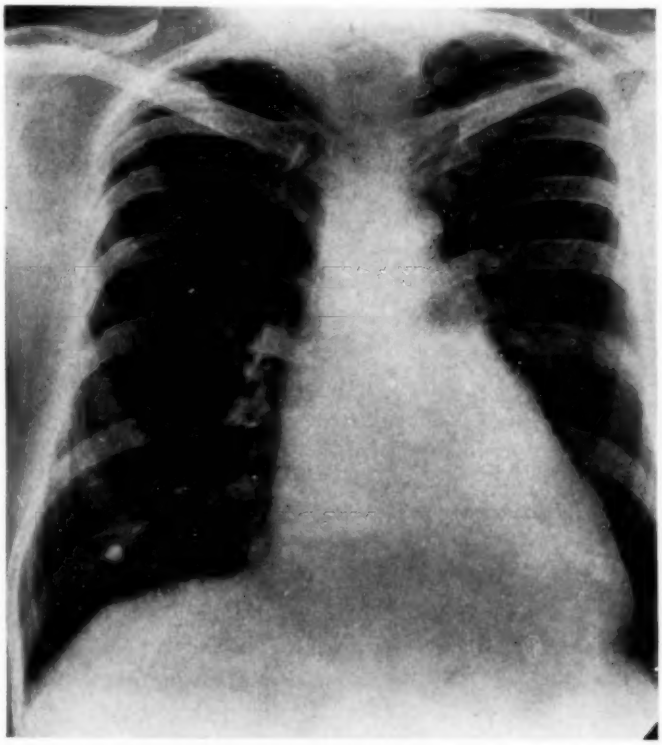

Fig. 2.—M.M., 50-year-old man. Rheumatic heart disease with "pure" mitral regurgitation. Unchanged cardiac silhouette for at least 25 years. Recent dyspnea due to onset of atrial fibrillation. Catheterization (after digitalization) revealed normal pressures in the left and right hearts and a cardiac output within the limits of normal.

The benign course of these types of mitral regurgitation may be due to the fact that little additional energy or oxygen is needed for the left ventricle to regurgitate blood into the low pressure left atrium (Braunwald, Welch and Sarnoff[1]). When, however, pulmonary arterial hypertension is present, the clinical pattern and course are entirely different.

Pulmonary arterial hypertension may

be produced by a large volume of blood regurgitating under high ventricular pressure through a wide open mitral valve. Such a train of events may develop rapidly after recovery from bacterial endocarditis:

L.G., aged 50, had a normal heart and lungs except for a faint apical systolic murmur. He developed bacterial endocarditis and recovered. He was left with severe mitral regurgitation, a large heart and roentgenologic and clinical evidence of pulmonary arterial hypertension and dyspnea on slight effort. Catheterization revealed pulmonary hypertension, left atrial systolic hypertension with an enormous V wave but no diastolic left atrial ventricular gradient. The forward cardiac output was low.

However, a diastolic left atrioventricular gradient is common in clinically pure mitral regurgitation and adds to the production of pulmonary arterial hypertension. Such a gradient results from diastole which is too short to permit sufficient emptying of the over-distended left atrium. This situation is abetted by anatomic mitral stenosis which is not infrequent in the adult with clinically pure mitral regurgitation. Actually, this group probably represents 30% of those who originally had evidence of mitral stenosis and regurgitation (Wilson[37]). Pulmonary arterial hypertension may also be due to left ventricular failure with or without pre-existing pulmonary arterial hypertension.

It is important to differentiate significant mitral regurgitation with pulmonary arterial hypertension from that with normal pulmonary artery pressure because prognosis and therapy may be different in the two.

Significant pure mitral regurgitation with or without pulmonary hypertension is characterized by a large left ventricle. The apical thrust is localized, forceful, poorly sustained and displaced laterally and downward. It is usually more prominent than the carotid arterial pulse. A pansystolic murmur is present which is widely transmitted and best to the left axilla. The electrocardiogram shows P mitrale or atrial fibrillation.

Pulmonary arterial hypertension not due solely to left ventricular failure is characterized clinically by a sternal systolic and pulmonary artery diastolic lift. P_2 is accentuated. These clinical findings may be present without roentgenologic or electrocardiographic signs of pulmonary arterial hypertension.

Roentgenologic signs consist of enlargement of the pulmonary artery segment and its branches. More severe instances are associated with dilated pulmonary veins in the upper lobes, more evident in the left upper lobe just above the left auricular region. Attenuation of the pulmonary branches in the lower lobes strongly suggests that some degree of pulmonary arterial hypertension is permanent (Fig. 3).

The electrocardiogram may fail to show the expected degree of leftward deviation of A_{QRS}. Right ventricular hypertrophy indicates that pulmonary arterial hypertension is severe.

In the absence of clinical evidence, pulmonary arterial hypertension is rarely significant and requires cardiac catheterization for detection.

The development of mitral stenosis implies that the rheumatic myocardial process and mitral regurgitation were not so severe as to prevent contact of the mitral leaflets. Pure mitral stenosis is the rarest form of mitral valve disease. In Wilson's series of 269 patients with the murmurs of mitral stenosis and insufficiency, in only four did the murmur of mitral stenosis persist and that of mitral regurgitation regress (Wilson[37]). The enlarged pulmonary segment creates an illusion of a small

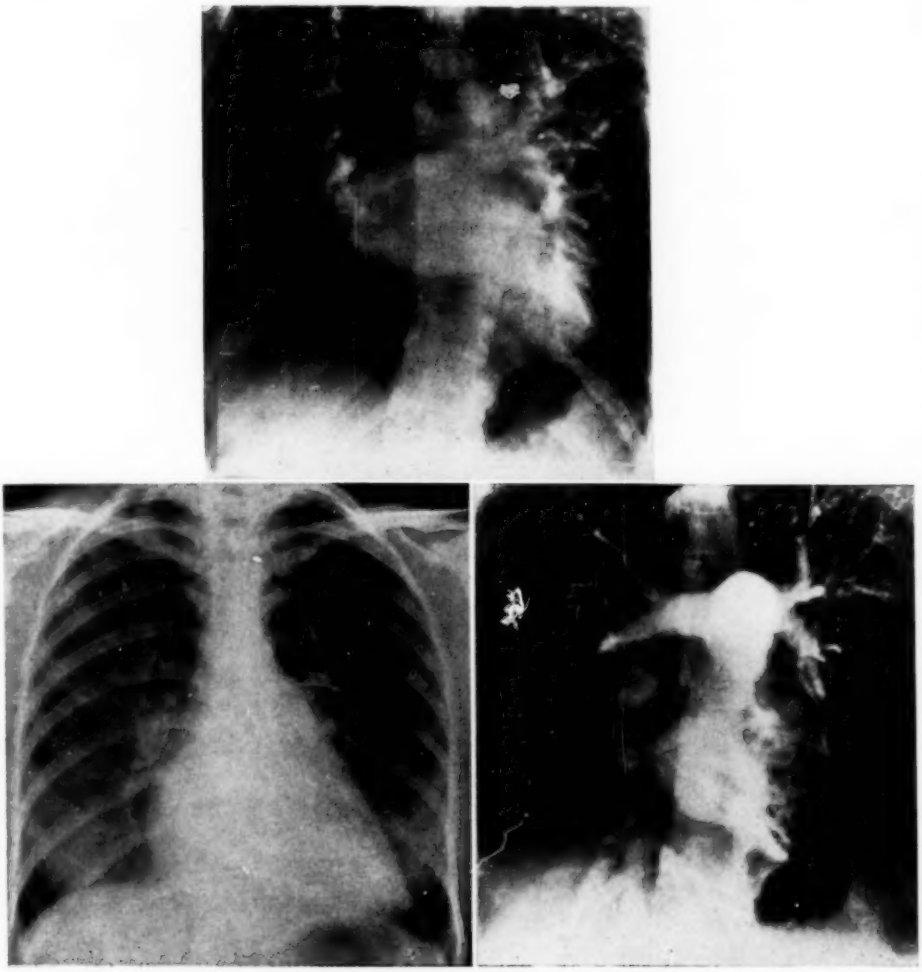

Fig. 3.—L.P., a woman, age 23 years, with severe pulmonary hypertension. Note increased vascularity in upper lobes and diminished vascularity in lower lobes verified by arterial and venous phases of the angiocardiographic study.

left ventricle just as it does that of a small aorta (Soloff, Zatuchni and Mark[32]). Angiocardiography indicates that the left ventricle may be distinctly larger than normal and may even be larger than the right ventricle (Fig. 4).

Mitral stenosis once formed tends to protect the left ventricle from overworking but burdens structures proximal to the block. The enlarged pulmonary artery is directly related to its pressure (Soloff, Zatuchni and Mark[31]). The right ventricle may not enlarge under the influence of pulmonary hypertension but once it surpasses twice normal in size, its volume is also related to pulmonary pressure (Soloff and Zatuchni[29]). Left atrial (Soloff and Zatuchni[27]) and right atrial volumes (Soloff and Zatuchni[29]) have no

significant relation to either pulmonary artery or left atrial pressures (Soloff and Zatuchni[28]). These discrepancies are an index of the intensity of myocardial damage independent of mitral block (Soloff, Zatuchni and Mark[31]). These anatomic abnormalities indicate that myocardial and mitral valve disease always co-exist in persons with rheumatic heart disease and mitral stenosis (Soloff, Zatuchni and Mark[31]). The primary effect of mitral obstruction is to raise pressure proximal to the block so as to maintain forward cardiac output. The primary effect of myocardial involvement is to depress forward cardiac output, perhaps partly due to tricuspid insufficiency of myocardial origin, but neither defect may be intense enough to produce measurable disturbance in function. Furthermore, one defect may influence the other. However, different degrees of involvement are not merely different stages of devolution but rather, as stated early, are patterns established in early adulthood and may remain unaltered for years or decades in the absence of associated illnesses (Soloff, Zatuchni and Mark[31]). The defects themselves, however, may predispose the subjects to associated illnesses.

Fig. 4.—F.K., age 43 years, mitral valvotomy 1952 for "pure" mitral stenosis with severe pulmonary hypertension; normal left and right intracardiac pressures and normal cardiac output in 1958. Note enlarged left ventricle which has remained unchanged since 1952.

These basic patterns can frequently be recognized on clinical grounds.

Mitral stenosis with normal heart size and normal P waves almost always means no measurable abnormality of pressure or cardiac output. If clinical symptoms raise the possibility of pulmonary hypertension, cardiac catheter-

ization is needed to prove its presence. On the other hand, P mitrale or atrial fibrillation indicate that significant rheumatic heart disease is present with or without mitral block. Functional mitral block as well as left ventricular failure are associated with pulmonary arterial hypertension. Although left heart catheterization may be needed to differentiate the hemodynamic pattern of the one from the other, clinical examination is usually decisive and frequently supported by roentgenologic and electrocardiographic evidence.

Pulmonary artery hypertension associated with mitral block produces the clinical and roentgenologic findings similar to that described under mitral regurgitation. The findings are frequently more obvious because very often the pressure is higher and the heart smaller. Left ventricular failure (in the absence of pre-existing pulmonary hypertension) is not associated with a systolic lift and radiologically shows true generalized pulmonary congestion. The dilated vessels may be partly obscured by extravascular fluid in the pleural space, interlobar fissures or in the hila. Kerley's lines are common to both left ventricular failure and mitral block. This difference in roentgenologic appearance has been attributed to differences in chronicity and permanency of the hypertension in the two states (Short[22,23]). This explanation is difficult to accept because chronic pulmonary congestion due to left heart failure does not change into the appearance of that seen in mitral block. Furthermore, severe pulmonary hypertension in mitral block can develop within several months even in the adolescent without passing through a stage resembling pulmonary congestion (Soloff[24]). These observations suggest that at least part of the pulmonary artery changes in the rheumatic subject is primary in the sense that it is not directly due to hemodynamic abnormalities within the heart.

Again, in the absence of clinical evidence, pulmonary hypertension is rarely significant and requires cardiac catheterization for its detection.

Pulmonary hypertension with or without a normal-sized heart is common. Primary myocardial disease without mitral block is uncommon. It is most commonly associated with atrial fibrillation (Fleming and Wood[9]) but the rhythm may be normal (Harvey *et al.*[13], Soloff, Zatuchni and Mark[31]). It is recognized clinically by an enlarged heart without a systolic sternal lift. Mitral block should not be diagnosed in such instances without confirmation by cardiac catheterization.

More frequently, both are present. Regardless of whether myocardial disease is entirely of rheumatic origin or has been aggravated by pressure, cardiac size does not significantly change nor does cardiac output significantly rise after mitral valvotomy (although stroke volume increases). The relative effects of both elements can be roughly judged by comparing cardiac size to the right ventricular systolic lift. Unfortunately, precise measurements require angiocardiography which permits estimation of right ventricular volume and cardiac catheterization which permits measurement of pulmonary hypertension and cardiac output. The larger the right ventricular volume and the lower the cardiac output, the more significant is myocardial disease and the less significant is mitral block.

The right ventricular volume is the most sensitive index of the extent of myocardial disease because it represents the combined effects of rheumatic myocardial involvement and pressure (Soloff and Zatuchni[29]). Unfortunately, its size cannot be determined by conventional roentgenol-

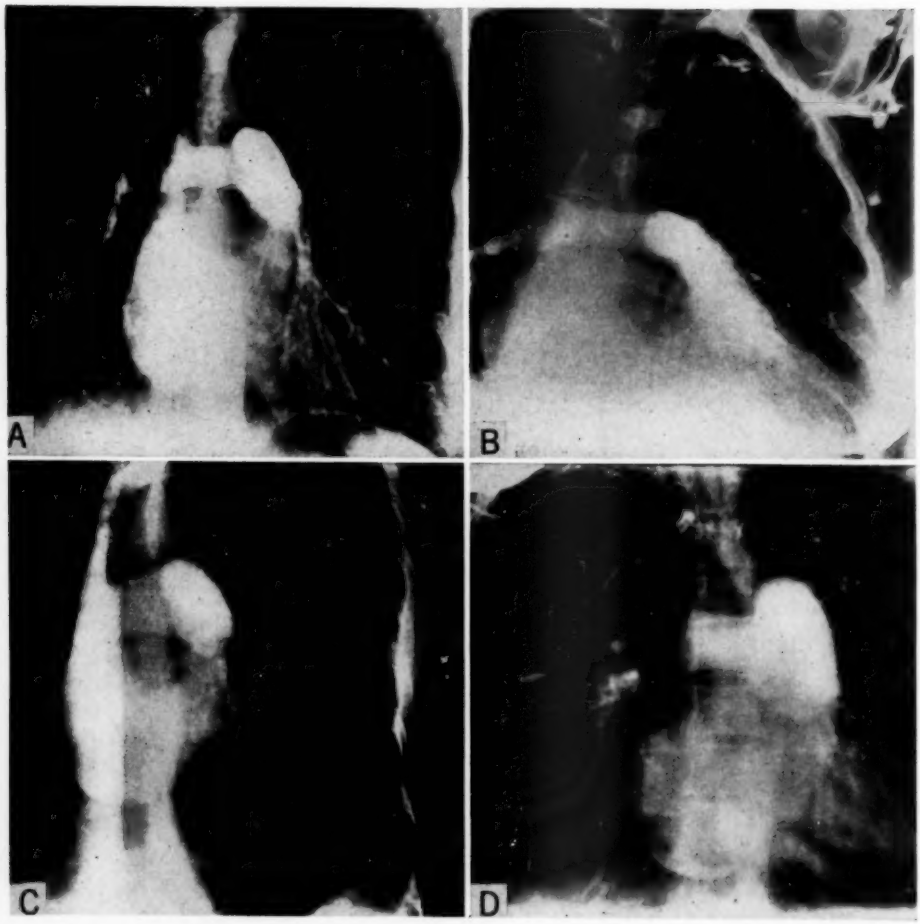

Fig. 5.—Angiocardiographic opacification of the right heart in 4 women in their early thirties. All had rheumatic fever in adolescence. All have mitral stenosis: a) normal pressures and normal cardiac output, b) normal pressures and decreased cardiac output, c) elevated left atrial and right ventricular pressures with normal cardiac output, d) elevated left atrial and right ventricular pressures and decreased cardiac output.

ogy nor indeed can that of the left atrium. Normally the right ventricle extends to the left border of the vertebral column in the posterior anterior view. In rheumatic heart disease, it may occupy the entire anterior surface of the cardiac silhouette (Fig. 5). The enlarged pulmonary segment is not a portion of the right ventricle and bulging of the ventral cephalic portion of the cardiac border in the right anterior oblique view in persons with rheumatic heart disease and mitral stenosis is due to displacement of the right ventricular outflow tract by the left atrium. Over-all cardiac size is a rough index of myocardial involvement.

The higher the pulmonary artery pressure, the smaller the right ventricular volume and the closer the output

to normal, the more striking are the clinical and laboratory results of adequate valvotomy. Increased right ventricular end-diastolic pressures are not, as claimed (Harvey and Ferrer[12]), a contraindication to valvotomy. On the contrary, such a finding unresponsive to medical therapy is an urgent indication for surgery provided cardiac output is normal or near normal. Such findings are particularly prone to occur in those with pre-existing pulmonary infarction. If cardiac output is markedly depressed and the right ventricular end-diastolic pressure elevated results following mitral valvotomy are usually not impressive.

A left atrial ventricular diastolic gradient may exist in the absence of pulmonary arterial hypertension (Samet *et al.*[20]). Its clinical significance, however, is questionable. Severe pulmonary arterial hypertension may be present even with the lowest cardiac output. It is therefore unlikely that clinical functional disability is due to such a gradient when pulmonary arterial hypertension is absent. Disability under such circumstances is predominantly or exclusively of myocardial origin.

Disproportionate enlargement of the right atrium is not uncommon (Soloff and Zatuchni[29]). Such enlargement suggests tricuspid regurgitation even in the absence of a characteristic pressure pulse. It is possible that the rare rise in forward cardiac output after valvotomy may be due to decrease in tricuspid insufficiency consequent to a decrease in pulmonary artery pressure. (McMichael and Shillingford[18]). This is suggested by complete disappearance of a pansystolic murmur of tricuspid insufficiency the day following open heart precise separation of adhesions of the mitral leaflets (Soloff[24]). Tricuspid regurgitation also makes it difficult to interpret a lack of forward cardiac flow after exercise. Indicator dilution tests may solve these problems.

On the other hand, significant complicating tricuspid stenosis is rare. This lesion should be suspected when a prominent presystolic wave is seen in the jugular pulse associated with a presystolic murmur waxing with inspiration and localized at the left lower sternal border. Electrocardiographic evidence of prominent right atrial P waves, first degree block and disproportionately little right ventricular preponderance confirms the clinical impression (Goodwin *et al.*[10]). When atrial fibrillation is present, cardiac catheterization is necessary to establish the presence of tricuspid stenosis.

Significant clinical improvement after mitral valvotomy is due to diminution or abolishment of pulmonary hypertension. Such a change can be brought about in at least four ways:

1. Decrease in mitral block with consequent decrease in back pressure.
2. Production of mild to moderate mitral insufficiency. Diminution in left atrial mean pressure decreases back pressure. The prognosis may be converted into that of the benign course of mild mitral regurgitation.

Both results decrease immediately the volume of blood within the distensible pulmonary arterial vessels and slowly permit regression of their medial hypertrophy.

3. Increased capacity of the cardiovascular system proximal to the block. Cardiac enlargement may occur after valvotomy. The enlargement has been attributed to enlargement of the left ventricle because of increased cardiac output. Actually the occasional increased cardiac output and more often the increased stroke output is too small to produce recognizable roentgenologic cardiac

enlargement. Angiocardiographic studies indicate that such enlargement (in the absence of gross and serious mitral regurgitation) is due almost exclusively to structures proximal to the mitral valve. The nature of this enlargement is not clear. It is possible that surgery may at times temporarily upset the equilibrium of subclinical rheumatic myocarditis (Soloff *et al.*[30]). It is unreasonable to anticipate immunologic reactions to a streptococcus as a result simply of trauma.

4. Decreased cardiac output. The effect may be associated with severe type 2 or 3, or both.

Most persons disabled by mitral valve disease have both mitral stenosis and regurgitation. The spectrum may vary from that resembling clinically pure mitral regurgitation to that resembling clinically pure mitral stenosis. The first is of no great diagnostic importance because direct vision surgery is indicated whether or not an element of stenosis is present. Correct diagnosis of the second at this time is important. A forceful localized poorly-sustained apical impulse and a third heart sound indicate the presence of significant mitral regurgitation. When these findings are absent, a pansystolic apical impulse suggests the presence of significant tricuspid regurgitation. This possibility is fortified by a loud first sound. The diagnosis may be verified by the effects of an intravenous infusion of norepinephrine (Soloff *et al.*[25]). This test has proved correct when all other technical studies suggested the presence of mitral regurgitation.

Finally, marked right ventricular enlargement may displace the left ventricle completely posteriorly and obscure a left ventricular impulse. Right ventricular hypertension may shorten the systolic murmur of mitral regurgitation. In these instances, leftward deviation of A_{QRS} as well as roentgenologic evidence of a ventricle which is enlarged and dips down behind the left leaf of the diaphragm are clues to the presence of significant mitral regurgitation. However, these latter findings may be obscured by pulmonary arterial hypertension. It is perhaps in these instances that indicator dilution techniques and other technical methods are needed to determine the presence and significance of mitral regurgitation. At this time it may be advisable to be prepared to proceed with direct vision surgery if digital exploration proves it necessary.

Mitral stenosis may also be associated with aortic valve disease. This combination should be the easiest to prevent because the aortic lesion is probably due to clinically recurrent rheumatic fever (Wilson and Linn[38,39]). It is especially important to detect the presence and severity of the aortic lesion, because if it is severe and uncorrected, mitral valvotomy may lead to disastrous mitral regurgitation.

Fortunately, the presence of aortic stenosis is easily recognized by the typical basal midsystolic murmur. Its severity, however, is not readily appreciated because the clinical and radiologic manifestations are dominated by the mitral lesion (Uricchio *et al.*[34]) (Fig. 6). Electrocardiographic deviation of A_{QRS} to the left and a prominent apical impulse when present are important clues to the presence of significant aortic stenosis.

Left heart catheterization is indicated to determine the severity of aortic stenosis whenever symptoms suggest the desirability of surgical correction of the mitral lesion. Angiocardiography is also extremely helpful. A thickened left ventricular wall indicates high-grade aortic stenosis even

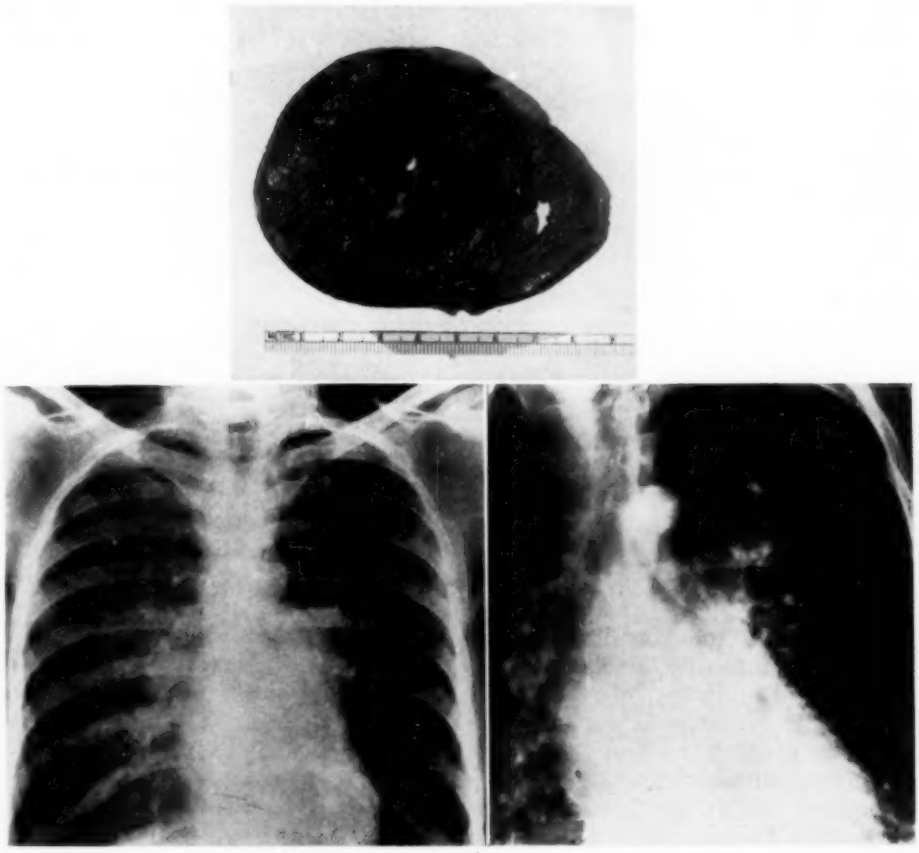

Fig. 6.—J.B., a man with mitral stenosis and aortic stenosis. Note dominance of mitral contour in conventional film. Note thick left ventricular wall in the angiocardiogram and the tremendously thickened left ventricular wall seen at necropsy.

if the left ventricular aortic gradient is not high (Soloff[24]).

Significant aortic regurgitation is rare in clinically pure mitral stenosis and is easily recognized by the peripheral signs of a systemic leak. However, almost always a diastolic murmur in the pulmonic region without peripheral signs signifies aortic regurgitation. This insufficiency frequently increases after mitral valvotomy. Such an increase may be due to greater stroke volume, the production of mitral regurgitation, a disturbance of the rheumatic equilibrium or a combination of these causes. Even if the heart enlarges, symptomatic improvement occurs so long as pulmonary hypertension has been decreased.

Aortic stenosis with regurgitation is also uncommon in clinically pure mitral stenosis and is more commonly associated with mitral regurgitation with or without mitral stenosis. The absence of pulmonary hypertension indicates that the aortic valve lesion is the dominant one. Angiocardiography helps to determine the dominant aortic

lesion (Soloff[24]). The smaller the left ventricular cavity and the thicker the left ventricular wall, the more dominant is the aortic stenosis. The larger the left ventricular cavity and the thinner the left ventricular wall, the more dominant is aortic or mitral regurgitation, or a combination of the two.

These combinations of valvular dysfunction are the most serious types of rheumatic heart disease and include the majority of rheumatic patients who die below the age of 50.

Clinically pure aortic stenosis is primarily a disease of late adulthood and has on the average the best outlook. Almost all instances below the age of 30 are of congenital origin. The older ones are frequently associated with atherosclerosis and coronary artery disease. It is for these reasons that left heart catheterization and angiocardiography are indicated to assess the hemodynamic disturbance of the aortic lesion whenever cardiac symptoms are present. There is no way at present to determine interference with coronary flow due to the deformed aortic cusps. A left ventricular aortic gradient and a thickened left ventricular wall are signs of functional block. When calcification of the aortic valve is absent and A_2 is normal, or when the subject is young, the possibility of supra- or infra-valvular stenosis should be excluded, if possible, by selective angiocardiography.

Clinically pure aortic regurgitation is the rarest rheumatic lesion. Nevertheless it is the easiest to diagnose because of the characteristic murmur and the striking peripheral manifestations. An associated lesion should always be sought if symptoms of cardiac insufficiency occur in the absence of an extremely large heart. Even a huge heart may be present for two or more decades in asymptomatic adults. This benign course may be due to the low peripheral resistance. However, just as in aortic stenosis, once symptoms are present in such persons, valvuloplasty would be desirable. Unlike aortic stenosis, no special techniques are needed in these instances because the clinical picture is unmistakable.

These then are the broad outlines which delineate the need for medical and surgical treatment of the failing rheumatic heart. It is important, however, not to underestimate the heart's tolerance to disease nor to exaggerate the benefits of therapy. Rheumatic pathologic anatomy once established and stabilized cannot be reversed at the present time by medical therapy. It is meaningless to compare surgical results to mortality statistics in rheumatic patients which were compiled years ago. The average death age in rheumatic valvular disease has increased by 6 to 8 years from 1927 to 1947 (Muller[19]) and has probably increased more since 1947. The new diuretics have postponed deaths from congestive failure and the antibiotics from infection. More important, the rise in hospital care of patients and particularly patients for whom new hopsital therapy is available has changed completely the type of rheumatic patient who is now hospitalized compared to those of years ago. It is for all these reasons that the prognosis of rheumatic valvular disease is far better than its reputation (Muller[19]).

Furthermore, although surgical treatment is obviously desirable for all gross mechanical defects which burden the heart, the artistic ability of the surgeon is still inadequate to cope with most of these lesions. This is true for most instances of aortic stenosis and insufficiency with or without stenosis and mitral stenosis and insufficiency with or without aortic stenosis or insufficiency, or both. All these

are the more serious lesions. Even pure mitral stenosis may not infrequently be uncorrectible by conventional means. This is the reason that surgeons are turning to other techniques such as the right-sided approach, transventricular approach with mechanical dilators and direct vision surgery. Even direct vision surgery at this time cannot always correct markedly deformed, fibrous or calcified valves and their supports.

It is for these reasons that the indications for valvular surgery at this time should be based upon clinical disability, with due respect to age, sex, occupation and social status, which is explainable on the presence of findings of hypertension attributable to distal valvular dysfunction.

When the clinical status appears too serious for surgery or the findings uncorrectible at this time by surgery, I_{131} may be administered (Eliasch *et al.*[8]). This drug may also be of value after unsuccessful surgery.

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SUMMARIO IN INTERLINGUA

Le Mechanismo del Corde Rheumatic in Discompensation e le Therapia Hodierne

Es describite le historia natural de febre rheumatic. Durante le passate cento annos le severitate de iste morbo ha decrescite, de maniera que hodie nulle mortes ab illo es incontrate in juveniles o adolescentes. Febre rheumatic clinic es un episodio o un series de episodios que tende a accelerar le subjacente chronic processo rheumatic. Proque tal occurrentias es rar post le adolescentia, le configuration de rheumatic morbo cardiac se monstra firmemente establite al etate de 20 annos.

Morbo rheumatic cardiac semper affice le myocardio e frequentemente etiam le valvulas. Le therapia medical consiste in (1) le prevention o eradication de un infection streptococcal, (2) le uso de corticosteroides pro myocarditis, e (3) le tractamento conventional pro discompensation que es resistente al therapia corticosteroidic. Therapia chirurgic es a recommendar in casos de incapacitate clinic debite a hypertension infra un valvula morbide. Le presentia de signos roentgenologic e electrocardiographic de un tal hypertension indica que le hypertension es plus avantiate e in parte irreversibile. Hypertension infra le valvula aortic debe esser verificate per medio de catheterisation del corde sinistre. Catheterisation del corde sinistre es essential in casos de morbo combinate del valvulas aortic e mitral. Significative indicationes additional del grado e del typo de implication in cata valvula es obtenibile per medio de angiocardiographia que permitte le mesuration del spissitate del pariete ventricular sinistre e del intensitate del activitate ventricular.

Quando le deformitates excede le arte hodierne del chirurgo o quando le stato clinic pare esser troppo grave pro permitter un intervention chirurgic, I_{131} pote esser empleate. Iste tractamento es etiam de valor si le therapia chirurgic non resulta in ulle melioration.

A NEW FACE OF TUBERCULOSIS*

By F. T. Roque, Lt. Col., MC, F.C.C.P.†

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Since the advent of chemotherapy the histopathology, clinical course, and prognosis of tuberculosis have been so altered that physicians and patients seem to have lost their fear of the disease. In the past 3 years with the use of high doses of isoniazid (INH) combined with paraaminosalicylic acid (PAS), or daily streptomycin (SM), or both, the infiltrations of pulmonary tuberculosis seen in roentgenograms have cleared so rapidly and even completely in some cases that the diagnosis has been changed to bacterial pneumonia. The danger of mistaking the rapid clearing tuberculosis of the lungs for pneumonia is great, especially if the etiological organisms cannot be recovered. This is a new face of tuberculosis, the subject of this paper.

Case Reports. Three such cases of tuberculosis of the lungs and one pleural effusion which have cleared as fast as bacterial pneumonia, if not faster, are here presented.

Case 1. This patient, a 50-year-old Caucasian male, Department of the Army civilian, was admitted to the hospital on 13 June 1959 with a diagnosis of primary atypical pneumonia. He had symptoms of cough with a small amount of expectoration, chest pain, and temperature of 102 to 104° F. He was treated with penicillin and broad spectrum antibiotics. After 3 days of intensive treatment the patient's condition remained unimproved. The tuberculosis service was then consulted. The chest films revealed caseo-nodular and caseo-exudative type of infiltrations, very characteristic of tuberculosis. The smears of the sputa did not reveal acid fast bacilli, but the first strength PPD was positive. The diagnosis was changed to: Tuberculosis, pulmonary, moderately advanced, right upper lobe, active. Upon transfer of the patient to the tuberculosis service all previous medications were discontinued. Instead, chemotherapy for tuberculosis consisting of INH 16 mg. per kg. (1400 mg.), PAS 12 gm., and pyridoxine 150 mg. daily was started on 18 June. Three specimens of gastric washings and three of sputums were cultured for acid fast bacilli. In the meantime the administrative wheels rolled swiftly, and on 7 July 1959 he was transferred to a tuberculosis sanatorium in his home state. On 25 July 1959 a letter was received from the patient giving the information that a chest film had been taken soon after his arrival there. It revealed that his disease had cleared considerably. Furthermore, he said that the doctors felt the disease had "cleared too fast for a tuberculosis diagnosis." They were seriously considering a diagnosis of lung abscess following pneumonia and not tuberculosis. In our reply to the patient we informed him that on 21 July 1959, a few days before receipt of his letter, we had forwarded to his sanatorium the results of cultures of three sputums and three gastric washings, which were *all positive* for *M. tuberculosis*.

The chest films of this patient were sent with him on his transfer to the United States. Since he stayed in our hospital only 19 days, the 30-day chest film routinely taken after start of chemotherapy was not obtained.

Case 2. This patient, a 30-year-old white woman, wife of an Army Officer, was admitted to the hospital on 5 May 1958. Two weeks prior to admission she tired easily, developed a cough productive of some whitish sputum, lost 6 to 8 lbs. of weight, had a low grade afternoon fever, and chest pain over the sternal region. On 2 May 1958 a chest film (Fig. 1), revealed caseo-exudative type of infiltrations in the left and right midlung fields. The extent of these infiltrations was minimal. The second strength PPD tuberculin skin test was positive. A previous chest

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film on 2 December 1957 was within normal limits. On the basis of the following facts, low grade evening fever, appearance of infiltrations typical of tuberculosis in roentgenograms, positive PPD skin test, and her 6 siblings ranging in age from 10 years to 9 months all being found positive reactors to intermediate strength PPD, the diagnosis of tuberculosis, pulmonary, minimal, bilateral, active, was made. The patient was therefore started on chemotherapy consisting of INH 12 mg. per kg. (600 mg.), PAS 12 gm., and pyridoxine 50 mg. daily on 5 May 1958, the day of her admission. A chest film (Fig. 2), on 5 June 1958, a month after chemotherapy, revealed complete clearing of the infiltrations in both midlung fields. The serial gastrics and sputum studies for culture of *M. tuberculosis* were negative. In spite of the failure to demonstrate *M. tuberculosis* in this patient, diagnosis of active pulmonary tuberculosis seemed justified based on the fact that all her 6 children, including a 9-month-old infant, were found to have positive tuberculin skin tests. Incidentally, all the children were placed on therapy of INH and PAS. At the receiving hospital in the United States where she was transferred, the diagnosis of tuberculosis was questioned. However, the chemotherapy for tuberculosis which she was getting was continued. As far as we know, she was kept on this treatment, although on an outpatient status.

CASE 3. This patient, a 26-year-old Japanese woman, wife of an Army enlisted man, was admitted to the hospital on 2 March 1959 because of cough and a fever of 102° F. of 5-days' duration. The chest film (Fig. 3), obtained on admission revealed extensive caseo-exudative infiltrations involving the right upper lobe from the apex to the third anterior rib. In the right first anterior interspace there was a cavity which measured about 2.5 cm. The extent of the disease was moderately advanced. The patient was placed on chemotherapy of INH 16 mg. per kg. (800 mg.), PAS 9 gm., and pyridoxine 50 mg. daily on 3 March 1959. Acid-fast bacilli were found in a smear of the admission sputum. The patient became asymptomatic on the third hospital day. The chest film (Fig. 4), on 1 April 1959, a month after chemotherapy was begun, revealed an almost complete resolution of the infiltrations, and the cavity was lost to view. Only fibrotic residuals remained in the apex. The report of the roentgenologist had this statement: "Because of the rapidity of the clearing of the infiltrations, bacterial pneumonitis should be considered." However, the diagnosis of tuberculosis in this case could not be shaken since the cultures of three sputums obtained

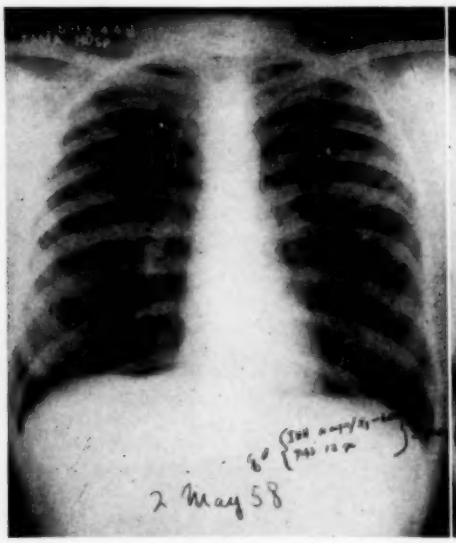

Fig. 1

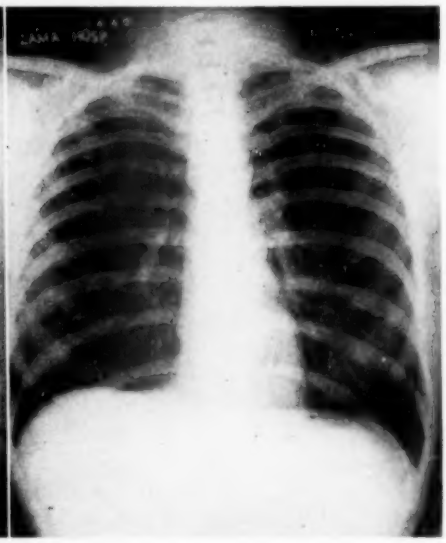

Fig. 2

in March and three gastric washings obtained in April were all subsequently found positive.

CASE 4. This patient was a 30-year-old Caucasian woman, wife of an Air Force officer. Early in March the patient felt a cutting pain in the left side of the chest. A chest roentgenogram was taken on 3 March 1958 which revealed blunting of the left costophrenic angle. Another chest film on 14 March 1958 revealed a slight increase in the shadow effacing the left base. She was referred to our Clinic on 17 April 1958 at which time a chest film (Fig. 5) was obtained which still showed the effacement of the left costophrenic angle, probably due to pleural fluid. A diagnostic thoracentesis was performed. A clear straw colored fluid, typical of tuberculosis effusion, was obtained. The intermediate PPD skin test was positive. A diagnosis of tuberculous pleural effusion was made, and the patient was started on chemotherapy of INH 12 mg. per kg. (800 mg.), PAS 12 gm., and pyridoxine 100 mg. daily on an outpatient basis. The chest film (Fig. 6) on 16 May 1958 revealed an almost complete clearing of the pleural effusion. Shortly afterwards the cultures of the pleural fluid were reported as positive for *M. tuberculosis*. This patient did so remarkably well on outpatient treatment that it was not found necessary to hospitalize her, and the chemotherapy was continued. The effusion never returned in spite of a pneumonia in the left lower lobe which she had in October, 1958. The pneumonia was treated successfully with intensive penicillin, also on an outpatient basis. The patient returned to the United States in March 1959 (normal rotation date of her husband) and was advised to continue chemotherapy for tuberculosis for a minimum of 18 months or until October, 1959. She was instructed to report to appropriate Air Force medical installation upon arrival in the United States where she should obtain supervision.

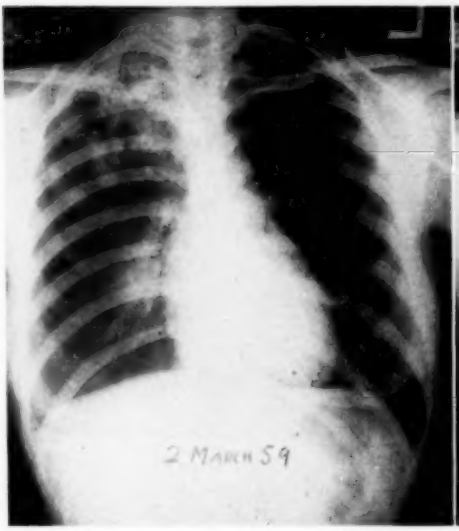

Fig. 3

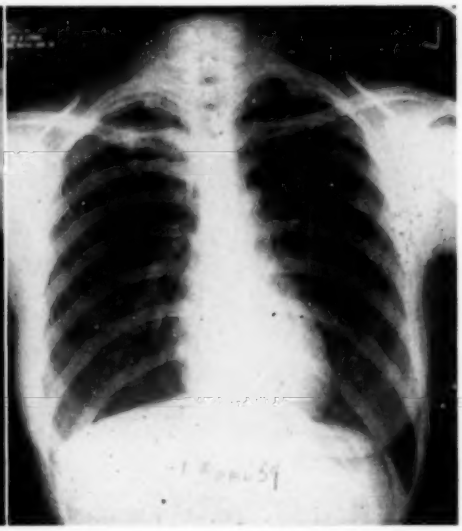

Fig. 4

Discussion. With these 4 cases it is not to be inferred that infiltrations in all active tuberculosis patients managed on high doses of INH will be cleared in about a month. It should be pointed out that in the cases discussed the disease was of recent development, and the patients had not been treated previously with chemotherapy for tuberculosis. They were all original treatment cases. The remarkably rapid clearing of the infiltrations may not occur in re-treatment cases and is not expected in disease which is old and predominantly nodular as revealed in roentgenograms.

It is our purpose in this paper rather to caution physicians, particularly those in general medicine and roentgenologists, not to rule out tuberculosis just because disappearance of the pneumonic infiltrations occurs as fast as ordinary pneumonia, if not faster. The clearing of the lesions might have been seen in the above cases sooner than about one month if chest films had been taken every few days or weekly from the start of chemotherapy, instead of monthly, which is the generally accepted routine in the follow-up of tuberculosis. If in tuberculosis treatment centers as those where the first two cases were sent, doubt was cast on the diagnosis of tuberculosis because the disease cleared so rapidly and bacterial confirmation was not available, it would be easy to see how a nonphthisiologist could be misled.

Conclusion. As a result of the use of high doses of isoniazid (10 to 16 mg. per kg. of body weight) in combination with daily PAS or SM, or both, in the treatment of pulmonary tuberculosis, complete clearing of the disease in about 30 days may occur. The danger of changing the diagnosis of such cases is pointed out, especially in those where the etiological organisms were not obtained.

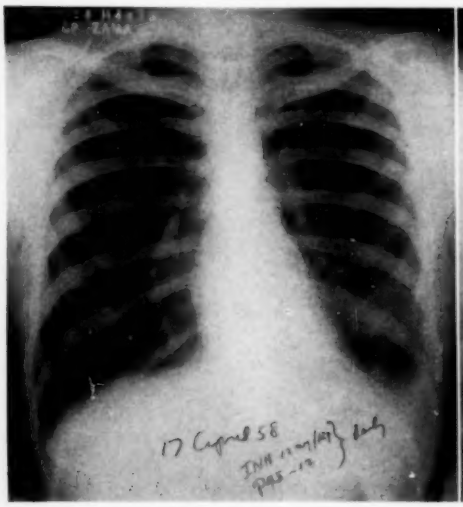

Fig. 5

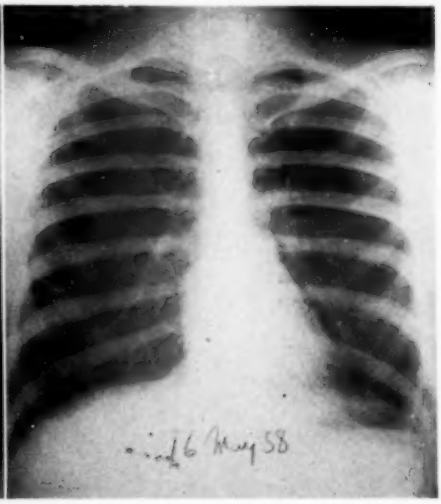

Fig. 6

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Un Nove "Physiognomia" de Tuberculosis

Como resultato del uso de grande doses de isoniazido (10 a 16 mg per kg de peso corporee) in combination con doses quotidian de PAS o streptomycina o de ambes in le tractamento de tuberculosis pulmonar, un complete resolution del morbo in approximativemente 30 dies es possibile. Es sublineate le periculo de alterar le diagnose in tal casos, specialmente in le casos in que le organismos etiologic non esseva identificate.

THE CLINICAL MANIFESTATIONS OF INFECTIOUS MONONUCLEOSIS
A REPORT OF TWO HUNDRED CASES

By Robert J. Hoagland, Colonel, MC
CHIEF, DEPARTMENT OF MEDICINE, MARTIN ARMY HOSPITAL,
FORT BENNING, GEORGIA

In 1946, after assignment to a military college, I had an opportunity to study many patients with infectious mononucleosis. After observing differences from statements in textbooks, I began, in 1949, to tabulate data concerning every patient. A report of a series of 56 personally studied cases was published in 1952[5].

Since observations of a greater number of patients might require modifications of opinions expressed in 1952, I continued to record data with the intent of reporting on a series of 200 personally examined patients. This report is the result of my own experience with every case of mononucleosis seen since 1949.

The clinical picture of any disease emerges most clearly if *one* physician examines, and also interrogates, *every* patient (not random, complicated, or referred cases), records observations and draws conclusions. Neither complete nor reliable information is acquired from retrospective review of clinical records of other, often less interested and experienced, observers.

Of the 200 cases in this series, 190 were inpatients, more desirable for repeated observations. There were a few females, only 19, because the patients were seen in Army hospitals (West Point, New York; Heidelberg, Germany; Fort Benning, Georgia). Pediatricians were requested to allow me to observe all children with serologically proven mononucleosis. However, only 3 cases in this series are children. All patients had blood smears and heterophil reactions characteristic of mononucleosis. Only 6 patients received corticosteroids.

Routine, and regularly repeated, investigations included blood counts, heterophil tests, electrocardiograms, tests for liver disease and urinalyses. Roentgenography of chest and spleen and the cardiolipin test were routinely done only once. Among the tests frequently, but not routinely, performed were throat cultures and paper electrophoresis of serum proteins. Liver biopsies were performed on a small series, with results which have already been reported (Hoagland and McCluskey[10]).

The medical literature contains tables of symptoms but few detailed reports of the clinical aspects of mononucleosis. Therefore, one purpose of this paper is to present a detailed description of mononucleosis as it evolves in hospitalized patients.

Since all patients had the characteristic blood smears and heterophil antibody reactions of mononucleosis, the clinical observations to be presented are unlikely to be alloyed by inclusion of illnesses with misleading similarities with mononucleosis. I have discussed the hematologic and serologic requirements for diagnosis elsewhere[5,6,7]. Readers are referred to Bender's excellent article[1] on these aspects of mononucleosis.

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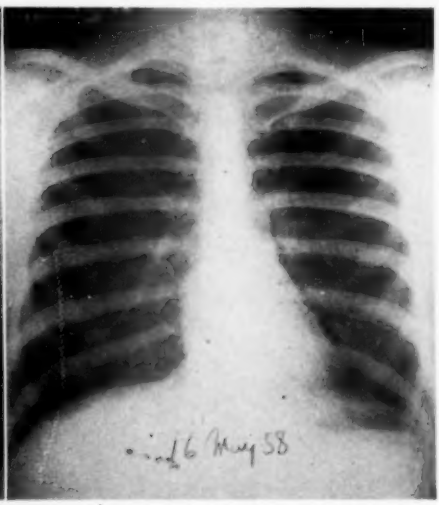

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lymphocytes must be present; (3) both of these features must be present over a period of *at least* 10 days. This last requirement will eliminate some viral disease which may produce transient lymphocytosis with atypical lymphocytes. Bender[1] believes that a minimal diagnostic level of atypical lymphocytes consists "of 20% or 1400 atypical lymphocytes near the time of the fever peak."

All patients in this series had characteristic heterophil antibody reactions: sheep cell agglutination titer of at least 1:56 in unabsorbed serum; a titer of at least 1:28 after absorption of serum with guinea pig kidney; and no agglutination after beef cell antigen absorption. (The method of reporting dilutions was altered during the course of this study; and lately a titer of 1:16 after absorption of serum with guinea pig kidney was considered minimal, although only one patient's absorbed serum agglutination titer was below 1:32.)

Of the 200 patients only 3 were children (6, 9 and 11 years of age); 4 were 14 to 16 years old. Only 2 were over 29 years: 31 and 35 years. The remainder, 191 patients, were 17 to 29 years of age. The picture of mononucleosis which emerges from this study may not be entirely representative, since patients with milder degrees of illness may not come to the attention of an Army inpatient service. On the other hand, civilians with a mild illness may not consult a physician, or if they do, the diagnosis of mononucleosis may be missed. One-third of the series (76 patients) were seen at West Point, where the local conditions permitted me to see most of the patients especially early in the illness, usually on the second or third day.

As far as I know, it has never been pointed out that mononucleosis is unusual among acute illnesses in that it evolves relatively slowly. Most uncomplicated acute diseases produce their characteristic symptoms and signs in 3, or fewer, days after onset; not mononucleosis. The unfolding of clinical manifestations will be described. Parenthetically, it is of interest also that whenever blood counts are characteristic of acute microbial diseases, they too usually appear within the first few days. In mononucleosis (not yet proved to be a microbial illness) characteristic blood counts are often delayed until the second week.

Inasmuch as mononucleosis has not been transmitted experimentally and since patients give no history of contacts with other patients, one can only speculate about the incubation period. However, there is considerable circumstantial evidence (which I have presented in detail)[8] casting doubt on reported epidemics and pointing to an incubation period of 33 to 49 days.

The clinical picture of mononucleosis becomes recognizable, and characteristic, as the days elapse. During the first 2 days, most patients experience only malaise. Even when medical attention is easily available, they are unlikely to consult a physician. Fever, chilliness and malaise increase; and sore throat and headache usually develop by the fifth day of illness. Physical examination at this time will usually reveal a fever around 100 to 101, slight posterior cervical and axillary lymph node enlargement and pharyngeal inflammation.

Although jaundice usually appears after patients have been ill more than 7 days, about 1 or 2% will seek initial medical attention because of jaundice.

Mononucleosis often increases in intensity so gradually that a patient may be unsure of the first day of illness. However, I was rarely unable to date the onset within a 2-day period.

Before describing the important

symptoms and signs in detail, 3 clinical syndromes will be proposed. The relative frequency of the syndromes does not apply exactly to the first week of illness since classification followed recovery.

TABLE 1.—CLINICAL SYNDROMES

Pharyngeal	80%
Typhoidal	12%
Icteric	8%

The *subjective* manifestations of mononucleosis are characteristic, but have little diagnostic value. The symptoms were usually mild or moderate in the first week; patients experienced malaise, but not prostration; fever was not extreme (see Fig. 1); patients often felt chilly, but rarely experienced chills; headache was rarely severe; jaundice was never intense.

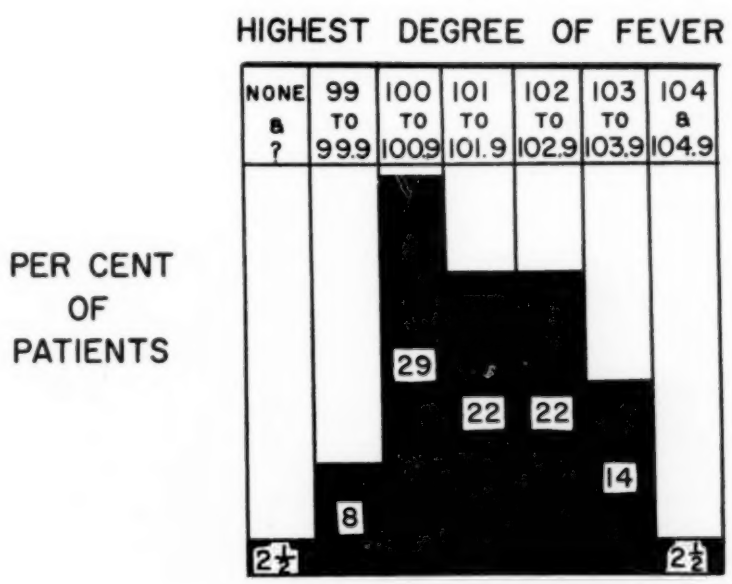

Fig. 1.

All patients had malaise and lymph node enlargement; all but 2.5% had a fever. It is possible that some or all afebrile patients had a slight fever before seeking initial medical attention. The presence of pharyngitis or jaundice determined classification.

Patients in the icteric category were those who were jaundiced at any time, regardless of pharyngitis. Non-icteric patients were placed in the pharyngeal class if they had signs of pharyngeal inflammation at some time. Patients in the typhoidal class had the basic symptoms but never had pharyngitis or icterus.

Sore throat was often a presenting complaint, but at times developed later. It usually increased in severity for about 3 to 6 days, was unaffected by antibiotics but was quickly alleviated whenever corticosteroids were administered. Not all patients with visible pharyngeal inflammation complained of sore throat, 76% of patients complained of sore throat, usually of moderate severity. Sore throat severe enough to interfere with swallowing of

water, and even saliva, was present in 11% of this series.

Some symptoms rarely, or never, encountered by me are stressed as of considerable value in militating *against* the diagnosis of uncomplicated mononucleosis. If encountered, the symptoms may indicate concurrent disease. These symptoms of considerable negative value are: chest pain, nasal discharge or congestion, paroxysmal or harassing cough, sputum, joint pains, painful or extremely tender lymph nodes, watery diarrhea (moderate increase of defecations occurred in 1% of patients), hematuria or dysuria, and severe abdominal pain. The misconception that mononucleosis may resemble acute appendicitis may have fatal consequences. This point has been discussed in another paper (Hoagland and Henson[9]). Physicians who have adequate experience with appendicitis and with mononucleosis are unlikely to have any difficulty in differentiating them.

TABLE 2.—PHYSICAL SIGNS

Lymph node enlargement		100 %
Fever		97.5%
Pharyngeal inflammation		83 %
Severe	25%	
Moderate:	34%	
Mild:	24%	
Eyelid edema		36 %
Palatal enanthem		25 %
Jaundice		8 %
Rash		3 %

A few of the above enumerated symptoms have been stated to occur in mononucleosis, in textbooks and in reports. Analysis of such reports would be space-consuming and tedious for most readers. Briefly, in many instances case reports antedated knowledge of the heterophil reaction; in other cases diagnosis of mononucleosis was made regardless of the heterophil reaction or without using absorption techniques; in a few cases diagnosis was based *exclusively* on a heterophil reaction; in a few cases two diseases probably co-existed; finally, in many cases authors referred to clinical observations of other persons.

The important physical signs observable at some time during the course of infectious mononucleosis are given in Table 2. Each merits discussion because there appears to be confusion concerning their frequency and significance.

Lymph node enlargement was invariably present at some time. Failure to detect lymph node enlargement is attributable to omission of daily examination of the neck. Enlargement was usually detectable by the end of the first week of illness. In 5 instances posterior cervical lymph node enlargement did not appear until the second week of illness. The latest appearance was on the twelfth day of illness. On the other hand, lymph node enlargement was the only subjective complaint for several days before other symptoms appeared in two instances. Duration of enlargement was variable. Usually the enlargement increased for 2 to 5 days, remained stable about 5 days and then slowly waned. Significant enlargement rarely persisted more than one month.

The cervical lymph nodes were always enlarged. Anterior cervical lymphadenopathy had little significance since it may be caused by any pharyngeal inflammation. Of diagnostic significance were enlarged posterior chains of cervical nodes, often palpable down to the clavicle. Enlargement of axillary and inguinal nodes was usually, but not invariably, present. Hilar lymph node enlargement was detected roentgenographically in only 3 instances; and it was not strikingly great.

Only 3% of cases had enlargement

which produced a "bull neck" appearance. The remaining patients had cervical node enlargement which I classified thus: mild, 37%; moderate, 50%; severe (but short of "bull neck" magnitude), 10%. Most of nodes classified as "mildly enlarged" were palpable but not visible. There was no correlation between degree of lymph node enlargement and degree of pharyngitis or duration of illness.

The following lymph node abnormalities were never observed: local heat and redness, marked tenderness (some patients may, of course, have a low threshold of tenderness), fluctuation or suppuration, unilateral involvement.

Pharyngeal inflammation varied in intensity as shown in the table. Exudate, usually spotty (infrequently involving the entire throat) was observed in 22% of cases. Hyperplasia of pharyngeal lymphoid tissue was almost always visible. The palatal arch and uvula often had a gelatinous appearance, but significant edema of the uvula was seen in only 2.5% of cases.

Pharyngitis usually appeared during the first week of illness, but onset in the second week was observed, albeit infrequently. I did not often attempt to find out, and record, precisely on what day pharyngitis occurred, so I cannot be more specific concerning this point. I only once observed pharyngitis occurring during the third week of illness. Usually pharyngitis increased in severity for several days, reaching its peak within 5, usually fewer, days, remained unchanged for 2 or 3 days and then rapidly subsided. Resurgence of inflammation, after return to almost normal, was observed only once.

Edema of eyelids was first mentioned in 1952 (Hoagland[5]). It consists of drooping of the swollen orbital portion of the upper eyelid upon the palpebral portion and sagging of the latter, which is also slightly swollen, resulting in a narrowed ocular aperture. One cadet stated that on the morning of admission a roommate had asked whether he was going to give his orders in Chinese because of the oriental appearance of his eyes.

Although present in less than half of the cases, eyelid abnormality was a helpful sign. There is great variability in appearance of eyes, so an examiner cannot be certain that a patient does not normally have sagging eyelids. I have the impression that eyelid edema usually occurred within the first 10 days of illness and lasted only about 3 days.

The *palatal enanthem* has aroused controversy as to diagnostic value and precedence of discovery. Paul[13], in 1939, briefly mentioned "petechiae on soft palate." I observed this sign early in my study of mononucleosis and wondered whether it might be specific for mononucleosis; it is not. I have seen a typical enanthem in a case of rubella. Nevertheless, when all other characteristic clinical features of mononucleosis are present, the appearance of this sign will almost certainly lead to the diagnosis of infectious mononucleosis. I have never seen the palatine enanthem in a mononucleosis suspect who did not also, sooner or later, have confirmatory blood smears and agglutination tests.

To clarify the appearance of this enanthem it was depicted in color photographs elsewhere[7]. It consists of round, *sharply circumscribed*, red spots 0.5 to 1.0 mm. in diameter. The sharp outlines differentiate these lesions from the enanthems of measles, rubella and other diseases. The lesions are probably petechiae because they are red at first, become brown in about 48 hours and disappear about 4 days after appearance. They were distributed fairly symmetrically, usually at the junction of the hard and soft palate.

I observed that the lesions were almost always seen between the fifth and twelfth days of illness, never before, and rarely as late as the seventeenth day. By examining the palate daily one observes that the lesions appear as "crops" over a period of about 36 hours. Characteristically, one spot will be seen during morning rounds, a few more will be visible in the evening, and the next morning the whole crop (usually 6 to 20 lesions) will have appeared. In 3 instances, a second crop appeared—4 to 9 days after the first.

Jaundice was observed in 16 patients. It appeared between the fourth and fourteenth day of illness (most often around the ninth day) except that once it appeared on the second and once on the twenty-first day of illness. Jaundice was usually mild, infrequently moderate, never severe. Ten patients were jaundiced when first examined by me. In some instances mononucleosis had been diagnosed or suspected. In other instances "viral hepatitis" had been diagnosed. The differential diagnosis, which was not difficult, will be the subject of a separate report.

Finally the physical sign which, in my opinion, actually has negative value: *rash*. A rash appeared in only 3% of cases. Two patients had a pink maculopapular eruption; the remainder had diffuse faint erythema. Since skin eruptions appear much more frequently in several other acute febrile diseases, it seems logical that their presence should cast doubt on the probability of mononucleosis. In another paper[5], I analyzed reports of much greater frequency of rash in mononucleosis and discovered that there was an inverse correlation between validity of diagnosis and incidence of rash. Interested readers are referred to this report for details.

The duration of illness was practically equivalent to the duration of fever. Of course, patients did not regain usual strength immediately. Speed of return of vigor was inversely proportional to length of illness. Prolonged convalescence was not observed in male patients.

Recrudescences after 2 to 3 afebrile days occurred infrequently; they lasted only 2 to 4 days. Relapses, after patients had been fever-free for 5 or more days, were never observed. Several patients stated that they had been told that they had had mononucleosis previously, but they knew little of the bases for the diagnosis. On several occasions I was able to obtain pertinent clinical records. The diagnosis of mononucleosis was never justified; indeed, sometimes it had not been made.

"Chronic mononucleosis" is a misconception which has been discussed previously[5]. Follow-up examinations of many patients at West Point, Heidelberg and Fort Benning revealed no bases for this concept.

In reading the medical literature one gets the impression that complications of mononucleosis occur frequently. Some complications result in dramatic symptoms, and they are often reported. The uncomplicated cases are usually unreported. From this series of 200 consecutive serologically proved cases, we can get a rough estimate of the frequency of complications. None occurred frequently.

One patient's spleen ruptured spontaneously; and he was operated on. Facial nerve paresis, a mild meningitis, salivary gland inflammation and complete atrioventricular heart block were, each, observed once. I saw no other complications. There were no deaths. Patients recovered completely from these complications, except that electrocardiographic evidence of atrioventricular block persisted, although the patient had no subjective manifesta-

tions of heart disease and was capable of strenuous exertion.

COMMENT. This report, of 200 cases, is the continuation of a study of mononucleosis, begun over a decade ago. All but 10 were inpatients. All were examined by me. Hematologic and serologic confirmation of the diagnosis was obtained in all cases.

In reading textbooks or articles one may get the impression that there is little use in paying much attention to clinical features of mononucleosis. This attitude springs from the fallacy that the clinical manifestations of mononucleosis are bizarre, anything goes, so to speak. The clinical manifestations observed by me were not manifold. Patients experienced feverishness of moderate degree, chilliness but rarely chills, malaise without prostration and, usually, sore throat. Symptoms which were rarely, if ever, present, and of considerable negative value were: nasal discharge or congestion, paroxysmal or harassing cough, sputum, pleuritic or other chest pain, severe abdominal pain, watery diarrhea, hematuria or dysuria and joint pain. In other words, mononucleosis does not have the earmarks of a respiratory disease, exclusive of pharyngitis, nor of gastrointestinal, urinary tract, cardiac or joint diseases. The symptoms, although not at all specific, were so uniform that interrogation alone helpfully guided our thoughts to, or away from, mononucleosis.

Physical signs were not "protean," as shown by the brevity of the list in Table 2.

Fever, with highest recordings usually between 100° to 102°, and generalized, relatively symmetrical lymph node enlargement were uniformly observed, except for a few afebrile patients, who may have had mild fever before seeking medical attention. Pharyngitis was seen in 4 out of 5 patients. Eyelid edema and palatine petechiae were present in one-third and one-quarter of the patients, respectively. The latter lesion is not specific for mononucleosis, but was a valuable clue in diagnosis. Eight per cent of patients were icteric. These observations led to classification into three syndromes: pharyngeal, typhoidal and icteric.

These personal observations of uniformity of clinical manifestations are the bases for my attempt to remove the adjective "protean" from its oft-repeated, but unjustified and incorrect, association with mononucleosis.

What are the explanations for the discrepancy between these observations and reports which stress the variability or unpredictability of mononucleosis?

First: many reports cited to bolster the "protean" concept antedate the discovery, in 1932, of the heterophil antibody reaction in mononucleosis. Second: many reports included cases regardless of results of serology. Third: some investigations included heterophil antibody reactions without use of the serum absorption techniques. Fourth: the diagnostic requirement of characteristic blood findings has, recently, been disregarded by several authors (Durfey and Allen[2], Fish and Barton[4], Hollister, Houck and Dunlap[11]), who described unusual or unprecedented clinical manifestations and achieved a paradox of nosology, namely, mononucleosis without mononucleosis! Two of these reports have been analyzed elsewhere (Editorial[3]). Fifth: uncritical, or unread, citing of older work exemplified by a recent paper (Fish and Barton[4]), which mentioned a British report of 1914 (Kirtland[12]) as a precedent for cardiac abnormalities in mononucleosis. In fact, however, the British article had nothing to do with mononucleosis; the British author stated clearly that he

was reporting on a streptococcal illness.

Summary. 1. The clinical manifestations of 200 consecutive, personally observed cases of infectious mononucleosis are analyzed. All but 10 were inpatients. All cases had characteristic hematology and heterophil antibody reactions.

2. Clinical features were fairly uniform, with lymph node enlargement present in all cases and pharyngitis in 4 out of 5. Eight per cent of patients were jaundiced. Three clinical syndromes are proposed: pharyngeal, typhoidal, icteric.

3. This large consecutive series of inpatients provided a chance to get an approximation of the frequency of complications. Only 5 complications were observed; none more than once. They were rupture of the spleen, facial nerve paresis, mild meningitis, salivary gland inflammation, and complete atrioventricular heart block.

4. Patients were usually febrile for 2 to 3 weeks. All recovered. Prolonged weakness or recurrence was not observed.

5. Five reasons for the discrepancy between these observations of clinical uniformity and the oft-repeated statement that mononucleosis is "protean" are presented. The chief of these is furnished by cases wrongly diagnosed, especially those without serological and hematological confirmation.

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SUMMARIO IN INTERLINGUA

Le Manifestationes Clinic de Mononucleosis Infectiose Un Reporto de Duo Centos Casos

1. Es analysate le manifestationes clinic, personalmente observate in 200 consecutive casos de mononucleosis infectiose. Omne le patientes, con 10 exceptiones, esseva hospitalisate. In omne le casos le hematologia esseva characteristic, e omnes habeva heterophilic reactiones de anticorpore.

2. Le aspectos clinic esseva satis uniforme. Allargamento del nodos lymphatic esseva presente in omne casos, pharyngitis in 4 ex 5. Octo pro cento del patientes habeva jalnessa. Es proponite le distinction de tres syndromes clinic, *i.e.*: pharyngee, typhoide, e icteric.

3. Iste grande serie consecutive de patientes hospitalisate provideva le opportunitate de obtener datos approximative con respecto al frequentia de complica-

tiones. Solmente 5 differente complicationes esseva observate, sed nulle plus que un vice. Illos esseva: Ruptura del splen, paresis del nerves facial, leve grado de meningitis, inflammation del glandulas salivari, e complete bloco cardiac atrioventricular.

4. Le patientes esseva usualmente febril durante 2 a 3 septimanas. Omnes se restabliva. Prolongate periodos de debilitate non esseva observate. Le mesmo valeva pro recurrentias.

5. Es presentate cinque rationes pro le discrepantia inter le hic reportate observation de uniformitate clinic e le frequente assertion que mononucleosis es un entitate de character "proteic." Le plus importante inter illos es le frequentia de diagnoses erronee, specialmente in casos non confirmate per studios serologic e hematologic.

SUMMARIO IN INTERLINGUA

(See page 30 for original article)

Un Controlate Studio Cec del Tractamento de Pneumonia Pneumococcal con Tetracyclina e con Tetracyclina Supplementate per Prednisolona 6-Methylic

Un controlate studio cec esseva executate in 42 patientes con pneumonia pneumococcal. Vinti-un recipeva tetracyclina in combination con prednisolona 6-methylic, durante que un gruppo comparabile de etiam 21 patientes recipeva tetracyclina sol. Le gruppo tractate con tetracyclina e prednisolona 6-methylic manifestava un plus rapide defervescentia del febre que le gruppo de controlo. Le datos roentgenoscopic esseva inconclusive. Un del patientes recipiente le duple medication moriva 8 septimanas post su admission al hospital con pneumonia del lobo dextero-inferior e insufficientia aortic. In iste patiente, qui esseva un alcoholico chronic, cirrhosis de Laennec e epilepsia post-traumatic fungeva como factores complicante e rendeva questionabile le relation directe inter su morte e le breve curso de prednisolona 6-methylic.

Occurreva nulle complicationes directemente attribuibile al uso de prednisolona 6-methylic.

Il existe nulle indication pro le uso adjunctive de steroides in le therapia de non-complicate pneumonia pneumococcal. Super le base del rapiditate con que le temperatura retornava a nivellos normal in le gruppo tractate con tetracyclina e steroide, il pare possibile que studios controlate va monstrar que steroides adrenal pote esser de valor in le tractamento de patientes toxic con alte grados de febrilitate.

A CONTROLLED BLIND STUDY OF PNEUMOCOCCAL PNEUMONIA TREATED WITH TETRACYCLINE AND TETRACYCLINE PLUS 6-METHYL PREDNISOLONE*

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The value of adrenal steroids as adjuvants to the chemotherapy of bacterial infections is equivocal. The general use of these agents in uncomplicated bacterial disease is not advocated. Certain infectious diseases, such as typhoid fever, brucellosis, severe tetanus, and Rocky Mountain spotted fever may be associated with a highly febrile toxic course. There is evidence that these patients may benefit from the administration of adrenal steroids along with appropriate and adequate antibiotic coverage (Lewis *et al.*[3], Magill, Killough, and Said[4], Smadel, Ley and Diercks[7], Woodward *et al.*[9], Workman *et al.*[10]). Experimental studies and clinical data show that the adrenal steroids, used alone or with inadequate antibiotic coverage in infections, may result in dissemination of the infectious process occasionally with fatal results (Kass and Finland[1], Romansky[6]). Surprisingly few controlled studies have been reported in infectious diseases on the use of adrenal steroids with adequate antibiotic coverage. One controlled study on an entity with a relatively predictable outcome, pneumococcal pneumonia, has been described (Wagner *et al.*[8]). It is not the purpose of this paper to review the relationship of adrenal steroids to systemic infections, which has been done by one of us and others (Kass and Finland[1], Romansky[6]), but present the data on a controlled blind study of pneumococcal pneumonia treated with tetracycline alone and tetracycline plus 6-methyl prednisolone.†

Methods. The diagnosis of pneumonia in the 42 patients in the study was confirmed by clinical, roentgenographic and laboratory evidence. Before starting therapy, direct smears of the sputum were stained by the Gram method. Sputum cultures, as well as aerobic and anaerobic blood cultures, were obtained before therapy was instituted. The study was composed of 2 groups of patients, 21 in each group. The control [illegible] received tetracycline alone and the [illegible] received tetracycline plus 6-methyl [illegible]e. The characteristics of these patients are summar-

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†Tetracycline and tetracycline plus 6-methyl prednisolone supplied as Panmycin and Panmycin plus Medrol through the courtesy of The Upjohn Company.

ized in Table 1. As noted in the table, the sputum smears of all 42 patients had large numbers of Gram-positive diplococci morphologically resembling the pneumococcus. Upon discharge, patients were requested to return to the clinic in 2 weeks for further clinical and roentgenographic evaluation.

TABLE 1.—A CONTROLLED BLIND STUDY OF PNEUMOCOCCAL PNEUMONIA. CHARACTERISTICS OF THE 42 PATIENTS IN THE STUDY

	Number of Patients on Tetracycline (21)	*Number of Patients on Tetracycline + 6-Methyl Prednisolone* (21)
Type of Pneumonia		
Lobar pneumonia	13	21
Bronchopneumonia	6	—
Negative chest roentgenogram	2	—
Age in years		
15-30	7	4
31-50	6	10
51-77	8	7
Females	5	7
Males	16	14
Coexisting conditions		
Arteriosclerotic heart disease	1	1
Chronic alcoholism	1	3
Asthma	—	3
Hypertensive cardiovascular disease	3	3
Bronchiectasis	2	1
Duration of symptoms before admission—days		
1-2	11	11
3-4	7	5
5-7	3	5
Temperature on admission		
103-105	12	7
101-102	9	11
99-100	—	3
White blood cells/c.mm. on admission		
1,000 or less	9	4
11,000-20,000	9	13
21,000-30,000	3	4
Gram positive for pneumococci	21	21
Sputum cultures		
Pneumococci	6	3
Nonspecific	15	18
Positive blood cultures for pneumococci	None	2

The tetracycline and tetracycline-steroid capsules were identical in appearance and given under a code number. Each capsule contained 250 mg. of tetracycline, or 250 mg. of tetracycline plus 4 mg. of 6-methyl prednisolone. The identity of the capsules was unknown until the end of the study. Both groups received 2 gm. of tetracycline per day, 500 mg. every 6 hours *per os* for a minimum of 5 days or until they were afebrile for a period of 48 hours. Those patients receiving steroids were given a total of 32 mg. of 6-methyl prednisolone on the first day, 16 mg. on the second and third days, and 8 mg. on the fourth day.

TABLE 2.—A CONTROLLED BLIND STUDY OF PNEUMOCOCCAL PNEUMONIA. SUBSIDENCE OF FEVER BY HOURS

Hours	*Number of Patients on Tetracycline* (21)	*Number of Patients on Tetracycline +6-Methyl Prednisolone* (21)
12	5	2
24	2	11
36	5	1
48	–	2
72	2	1
84	2	–
96	3	1
120	1	–
124	–	–
148	1	–

Results. The more rapid defervescence of fever in the tetracycline-6-methyl prednisolone-treated patients was the most noticeable feature of the study. This defervescence of fever is illustrated in Fig. 1 and summarized in Table 2. In this group, 3 patients had temperatures of 99° F. on admission and did not become febrile after the institution of therapy. Of the remaining 18 patients, 13 (72.2%) were afebrile by 24 hours after initiation of therapy and 3 additional patients became afebrile within 48 hours. Hence, 16 patients (88.8%) were afebrile in 48 hours after the institution of anti-

biotic-steroid therapy. The 2 remaining patients became afebrile in 72 and 96 hours.

In the control group of 21 patients, 7 (33.3%) were afebrile 24 hours after therapy was begun. Five more were afebrile in 36 hours and no additional patients were afebrile at the end of 48 hours. Thus, a total of 12 patients (57.1%) were afebrile within 48 hours after the therapy was instituted. Of the remaining patients, 2 became afebrile in 72, 2 in 84, and 3 in 96 hours. One patient became afebrile on the fifth day and another on the seventh day.

In the tetracycline-steroid-treated group, temperature elevations occurred in 2 patients after afebrile periods of 1 and 2 days. The temperature did not exceed 101° F. and occurred while they were receiving the 6-methyl prednisolone. The patient who had a recurrence of fever 1 day after becoming afebrile, subsequently developed a pleural effusion and had an unresolved pneumonia. This patient will be discussed in more detail. The other patient suffered no complications. No recurrence of fever was noted after the 6-methyl prednisolone was discontinued.

In the control group, in 3 patients a single spike in fever occurred after afebrile periods of 11 and 3 days in 2 patients and 1 day in a third. This single spike in the temperature course of the 3 control patients did not exceed 102° F. and was an isolated finding not associated with a suppurative complication or clinical relapse.

A comparison of the roentgeno-

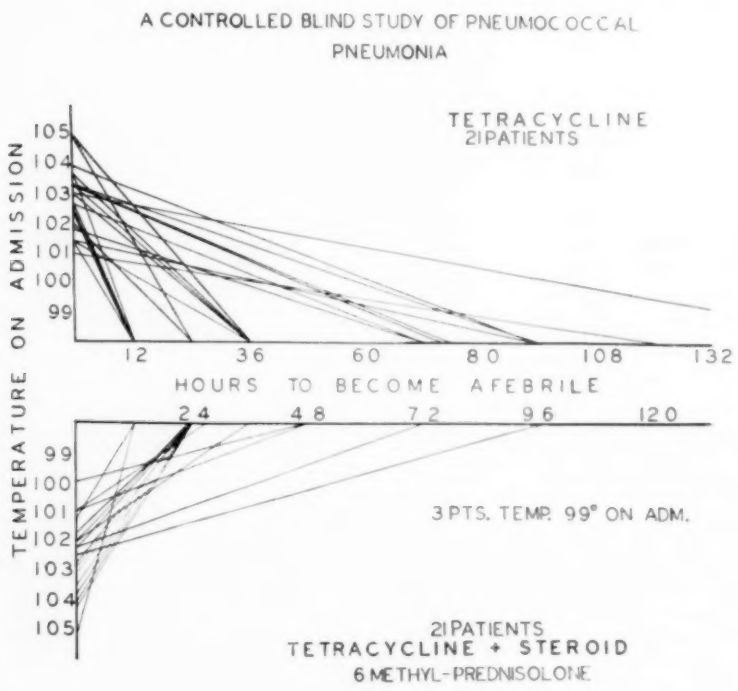

Fig. 1

graphic results in the 2 groups (Table 3) was not as noticeable as the response in fever. In the tetracycline-6-methyl prednisolone-treated group, 9 patients had complete resolution of the pneumonia by chest roentgenogram. This resolution took place between the third and eleventh days after therapy was instituted. Ten patients showed significant resolution of the pneumonic process during their period of hospitalization. Follow-up was available in 1 patient in this group and the chest film was completely clear 22 days after discharge. In 2 patients no resolution had taken place by the time of discharge. Follow-up was available in 1 patient who was readmitted 8 weeks later and died. This patient is discussed in more detail under complications.

TABLE 3.—A CONTROLLED BLIND STUDY OF PNEUMOCOCCAL PNEUMONIA. DEGREE OF RESOLUTION OF PNEUMONIA IN THE 42 PATIENTS

	Number of Patients on Tetracycline (21)	*Number of Patients on Tetracycline + 6-Methyl Prednisolone (21)*
No change or minimal clearing	4	2
Marked resolution	11	10
Complete resolution	4	9
Negative on admission	2	–

In the control group, 4 patients had complete clearing of the pneumonia by the fourth, seventh, ninth, and tenth days after therapy was begun. Significant resolution of the pneumonia by roentgenogram was observed in 11 patients. Follow-up examination was available in 3 instances in this group. Complete resolution had occurred in 1 patient who returned 50 days after discharge, nearly complete resolution in another in 26 days, and no significant change in a third who returned 11 days after discharge. Of the 4 patients classified as having no change in their chest roentgenogram during their period of hospitalization, follow-up examination was available in one. In this patient no significant resolution was noted 22 days later.

No significant difference in laboratory findings was observed in either group.

COMPLICATIONS. Suppurative complications such as empyema, meningitis, and pericarditis did not occur in either group. One patient in the tetracycline control group had persistent pleuritic pain for 3 days after therapy was instituted. No further complications occurred in this patient.

A minimal pleural effusion not requiring thoracentesis with subsequent spontaneous reabsorption occurred in 1 patient in the control group and in 1 patient in the tetracycline-steroid group.

No deaths occurred in either group during the course of the study.

One patient in the tetracycline-steroid-treated group died 8 weeks after discharge. This patient was a 31-year-old Negro man admitted with a right lower lobe pneumonia and blood cultures positive for a pneumococcus. He was a known chronic alcoholic with marked hepatomegaly who also had epilepsy as a sequel to the evacuation of a subdural hematoma 5 years prior to this admission. The patient became afebrile 3 days after tetracycline plus 6-methyl prednisolone therapy was instituted, however, a single spike in temperature to 101° F. occurred on the fifth day. The 6-methyl prednisolone-tetracycline combination was discontinued on the sixth hospital day. He received an additional 4 days of tetracycline, 2 gm. per day, and remained afebrile. Despite his asymptomatic and afebrile course, physical ex-

amination and chest roentgenogram revealed fluid in the right pleural space on the fifteenth hospital day. Thoracentesis at this time yielded 300 ml. of straw-colored fluid which was sterile on culture. No reaccumulation of fluid occurred roentgenographically. There was no significant change in the right lower lobe infiltrate by the nineteenth hospital day. He was afebrile and asymptomatic when discharged to follow-up in the outpatient clinic on the twentieth hospital day with a diagnosis of slowly resolving pneumonia. He failed to return to the clinic and was readmitted 8 weeks after discharge with the symptoms, signs, and roentgenographic findings of an active right lower lobe pneumonia and aortic insufficiency. The patient died 24 hours after admission despite adequate penicillin therapy. Permission for postmortem examination was not obtained.

Complications that could be directly attributed to the steroid were not observed, such as gastrointestinal hemorrhage, severe electrolyte imbalance or disturbances of mood and orientation.

Discussion. In this study, the 21 patients treated with 6-methyl prednisolone in decreasing amounts over a 5-day period with 2 gm. tetracycline per day showed a more rapid defervescence of fever than a similar group treated with the same amounts of tetracycline alone. No "recurrence" or "rebound" of fever was noted upon the discontinuance of the 6-methyl prednisolone, nor was there an instance of hypothermia with the initial dose of steroid therapy as observed by Wagner *et al.*[8], in a similar study. The roentgenographic response in the tetracycline-6-methyl prednisolone group, as compared to the control group, was not as conclusive as the defervescence of fever. Despite the larger number of patients in the tetracycline-6-methyl prednisolone-treated group showing complete resolution of their pneumonia, the actual number of days to complete clearing had essentially the same distribution as the control group. No significant conclusions can be drawn from a comparison of those patients classified as having significant clearing of their chest roentgenogram due to the approximately equal numbers in each group and the lack of follow-up. During the period of hospital observation, 4 patients in the control group and 2 patients in the tetracycline-6-methyl prednisolone group failed to show improvement roentgenographically. These results are considered inconclusive, due to the small numbers in this category.

Complications in both groups were minimal except for the incident in the tetracycline-steroid group of the patient who developed a 300 ml. pleural effusion on the fifteenth day and whose right lower lobe pneumonia failed to respond despite clinical remission. This patient's death 8 weeks later from a recurrent severe right lower lobe pneumonia and aortic insufficiency is somewhat difficult to attribute directly to the short-term course of 6-methyl prednisolone some 2 months before, but it does introduce a precautionary note.

Lepper and Spies[2], in a controlled study using appropriate antibiotic therapy with hydrocortisone in the treatment of meningococcal and *H. influenzae* meningitis, concluded that no benefit could be expected from the routine employment of steroids in these diseases.

Wagner *et al.*[8], in a controlled study of 113 patients with pneumococcal pneumonia, 52 of whom received penicillin and hydrocortisone and 62 who received penicillin alone, felt that "the symptomatic benefit of hydrocortisone and the absence of any evidence to indicate the aggravation of the infectious process in pneumococcal pneu-

monia justified further cautious exploration of adrenal steroids as adjuvants to specific antibiotic therapy."

Petersdorf and others[5] from the same institution in a controlled study on pneumococcal pneumonia treated with penicillin and aspirin concluded that there was no difference in the rapidity with which the fever defervesced. Symptomatically, patients who received aspirin seemed to improve more rapidly during the first 24 hours than did the controls but there was no detectable difference beyond the first day.

It would appear from this study that there is no indication for steroids in conjunction with antibiotics in the treatment of uncomplicated pneumococcal pneumonia, but additional controlled studies are needed on the effect of adrenal steroids and antibiotics in patients who are highly febrile and "toxic."

Summary and Conclusions. A controlled blind study was carried out on 42 patients with pneumococcal pneumonia; 21 patients received tetracycline plus 6-methyl prednisolone and a similar group of 21 patients received tetracycline alone. The tetracycline-6-methyl prednisolone-treated group showed a more rapid defervescence of fever than the control group. Roentgenographic findings were inconclusive. One patient treated with tetracycline and 6-methyl prednisolone died 8 weeks after his initial hospitalization with a right lower lobe pneumonia and aortic insufficiency. The complicating factors in this patient of chronic alcoholism, Laennec's cirrhosis and posttraumatic epilepsy cast some doubt on the direct relationship of his death to the short course of 6-methyl prednisolone.

Complications directly attributable to the 6-methyl prednisolone did not occur.

There is no indication for adjunctive steroid therapy in uncomplicated pneumococcal pneumonia. On the basis of the rapidity with which the temperature returned to normal in the tetracycline-steroid-treated group, controlled studies may show the adrenal steroids to be of value in the highly febrile toxic patient.

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(Interlingua on page 29)

THE BLOOD DONOR: I. WHO ARE OUR BLOOD DONORS? AN ANALYSIS OF SOCIAL AND OTHER CHARACTERISTICS OF 12,759 DONORS*

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Most persons concerned with blood transfusion services doubtless feel, as we did when the problem was first presented, that the answer to the question, "Who are our blood donors?" is obvious and simple. When the question was considered more carefully, it was realized that our impressions were based on good personal knowledge of only a relatively few donors and that a truly satisfactory answer could not be given. Furthermore, interest in obtaining a good answer had been piqued by comments reaching us from a number of sources to the effect that there were real differences between the paid donor and the replacement donor, with the inference that the latter was a safe and reliable donor and that the reverse was likely true of the former. The validity of this expressed feeling was a matter of serious concern, for we have made liberal use of paid donors for some years. They currently comprise 60% of our total donor use.

Method. A survey of blood donors was undertaken to determine what kind of people were providing us with blood. To obtain a representative sampling of the donor population geographically, seasonally, and numerically, the study was carried out on all donors accepted during 5 one-week periods, selected during the months of February, April, June, August, and November, 1958, in 12 cities where we operate major community blood banks. The cities were: Phoenix, Arizona; Albuquerque, New Mexico; El Paso, Houston, San Antonio, Lubbock, and Harlingen, Texas; Meridian, Mississippi; Little Rock, Arkansas; Cheyenne, Wyoming; Reno, Nevada; and Alexandria, Louisiana. The special inquiries for the survey were made by the screening secretary in each bank as a part of the usual donor questioning, and information was obtained from all donors accepted during each of the 5 weeks selected.

It is important to understand that an abundance of donors is available, so that the most careful screening can be done and only those persons who are quite acceptable from both a medical and a personal standpoint are taken. It was judged that several items of information would be useful, and cards were prepared for entry of the information shown in Table 1. Thus, the study provided data for each donor as to the number of previous donations, the place and reason for the first blood donation, the occupation, current employment status, whether or not a permanent resident of the area, whether this donation was as a paid or replacement donor, and the donor (blood unit) number assigned to the current donation.

In relation to grouping of the answers to question 4, U.S. Census Bureau reports were utilized[2]. To obtain complete data by occupation for the 8 states included in the study, it was necessary to go back to the last complete U.S. Census, which was taken in 1950. This enumerates the total labor force, 58.3% of the total population, and breaks it into 10 major occupational groups by states. Data

*The assistance of the Bureau of Vital Statistics, Arizona State Department of Health, in reviewing the data is gratefully acknowledged.

for the 8 states in the study are shown in Table 2. The occupations are listed in order of approximate average annual income, based on U.S. Census figures. Although the labor force has increased numerically since the 1950 figures, available information indicates that the percentage relationships of the ten occupational groups have not changed significantly. Table 3 expands these key groupings by showing examples of the exact occupations in each group. Since there are three

TABLE 1.—DONOR QUESTIONNAIRE

The following information was obtained from each donor:

1. How many times have you given blood?
2. Where did you first give blood?
   a) Southwest Blood Bank
   b) Other Blood Banks
   c) Red Cross Regional Center
   d) Military Blood Center
3. Why did you first give blood?
   a) Paid Donor
   b) Replacement
   c) Volunteer to Red Cross
   d) For Military Use
4. What is your occupation? (13 categories, see Table 2)
5. Are you presently employed?
6. Are you a permanent resident of the area?
7. Are you replacing blood for someone?
8. The donor number assigned.

other categories of persons who frequently are blood donors, these were added to the 10 census groups: Servicemen (active members of the Armed Forces), housewives, and college students. Regarding question number 6, donors were considered as permanent residents if they had resided in the local area for at least one year or stated that they had established the locale as a permanent residence. Members of the Armed Services were arbitrarily classified as permanent residents because they normally are assigned a tour of duty exceeding one year.

A total of 12,759 donors were included in the survey; 9,701 (76%) were paid donors and 3,058 (24%) were replacements (Table 4). Our percentage of total replacement donors in this same year was 40%. It is believed that the lower percentage in the study group is due to the fact that many of the replacement donors are bled in the 65 hospital drawing stations which are operated by our central blood banks where the surveys were made, whereas all of the paid donors are drawn in the central banks. In analyzing the results, all data were calculated separately for both the paid-donor group and for the replacement donors; then both groups were combined to obtain data for the entire group as the basis for evaluating how far either group might be from the average, or from each other. The group in the study represents a 10.3% sample of the total donors drawn during the study period (123,475); the paid-donor group is a 13.1% sample, and the replacement group a 6.3% sample. Statistically, this represents a significant sample from which conclusions may be made concerning the total donor population, because the characteristics brought out are substantiated either by the presence or absence of rather large differences.

TABLE 2.—OCCUPATION OF EMPLOYED PERSONS* IN THE 8 STATES IN STUDY, 1950 CENSUS

Income Rank	*Occupation Group*	*% of Employed Persons*
1	Professional-Technical	7.8
2	Managers, Officials, Proprietors	9.0
3	Sales	6.6
4	Craftsmen, Foremen	12.0
5	Clerical	9.4
6	Operatives	14.2
7	Service Workers	11.2
8	Laborers	6.8
9	Farmers	13.3
10	Farm Laborers	5.2

NOTE: a) Because of their frequency as blood donors, the categories of *Servicemen*, *Housewives*, and *College Students* were added to the 10 in the Census study.
b) Occupation not reported for 4.5% of those employed.

*"Statistical Abstract of the United States," Bureau of the Census, U.S. Department of Commerce (1958 Edition) (Tables 279 and 410).

Results. DONOR OCCUPATIONS. Figure 1 demonstrates the distribution of the study group by occupation, showing the percentage of each occupation in the 3 groupings of the donors: the total study group, the paid donors, and the

TABLE 3.—EXAMPLES OF EMPLOYEES IN THE VARIOUS CENSUS BUREAU CLASSIFICATIONS*

PROFESSIONAL-TECHNICAL

Accountant
Actor
Pilot
Artist
Chemist
Clergyman
Physician
Draftsman
Engineer
Lawyer
Musician
Nurse
Teacher
Technician

CRAFTSMEN-FOREMEN

Carpenter
Electrician
Machinist
Mechanic
Plasterer
Plumber
Metal Worker
Foreman
Brickmason
Boilermaker

CLERICAL

Bookkeeper
Clerk
Telephone Operator
Stenographer
Secretary
Typist
Mail Carrier
Cashier
Collector
Office Machine Operator

FARMERS

Farm Owner
Farm Tenant
Farm Manager

OPERATIVES

Bus Driver
Seaman
Taxicab Driver
Truck Driver
Meat Cutter
Deliveryman
Chauffeur
Apprentice
Switchman
Stationary Fireman
Machine Operator
Mine Operative Laborer

SALES

Salesman
Sales Clerk
Advertising Agent
Demonstrator
Insurance Agent
Real Estate Agent

SERVICE WORKERS

Hospital Attendant
Barber
Bartender
Housekeeper
Cook
Elevator Operator
Fireman
Janitor
Policeman
Waiter
Waitress
Porter
Fountain Worker

MANAGERS-OFFICIALS-PROPRIETORS

Buyers-Purchasing Agents
Department Heads
Inspector
Superintendent
Postmaster
Union Official

LABORERS

Common Labor
Fisherman
Gardener
Lumberman
Longshoreman
Car Washer
Car Greaser

FARM LABORERS

Farm Laborer
Farm Wage Worker

*"Statistical Abstract of the United States," Bureau of the Census, U.S. Department of Commerce (1958 Edition).

replacement donors. It is of interest that 78% of the donors are from only 5 of the 13 occupational groups (Craftsmen, 21%; Laborers, 19%; Armed Forces, 14%; Operatives, 14%; and Service Workers, 10%), and that these groups represent, country-wide, about 48% of those employed, including the Armed Forces (approximately 4% of the total labor force in 1957). It will be noted that these people are in the middle income brackets and that they provide 83% of the paid donors and 62% of the replacements.

Among the 13 occupational groups, the following give blood appreciably

more often as paid donors: Laborers, Operatives, and Service Workers. The groups donating appreciably more often as replacement donors are: Professional-Technical, Sales, Clerical, Housewives, Managers, and Farmers. However, together the latter groups comprise only 20% of the total donor population and but 34% of the replacements, but they represent 40.9% of employed persons (excluding the Housewives). They include both the highest and the lowest income groups. It is noteworthy that the 2 highest income groups actually gave more often as paid donors than as replacements, 485 and 428 donations respectively, although their percentage among paid donors is smaller than among replacements. Occupational groups donating with about equal frequency as paid and replacement donors are: Craftsmen, Armed Forces, Students, and Farm Laborers. One may conclude that: 1)

TABLE 4.—RELATIONSHIP OF DONORS IN STUDY TO ANNUAL DONATIONS

Total Donors (In Study)—	12,759	
Paid—	9,701	(76%)
Replacement—	3,058	(24%)
Total Donors (During Study Period)—	123,475	
Paid—	73,995	(60%)
Replacement—	49,480	(40%)

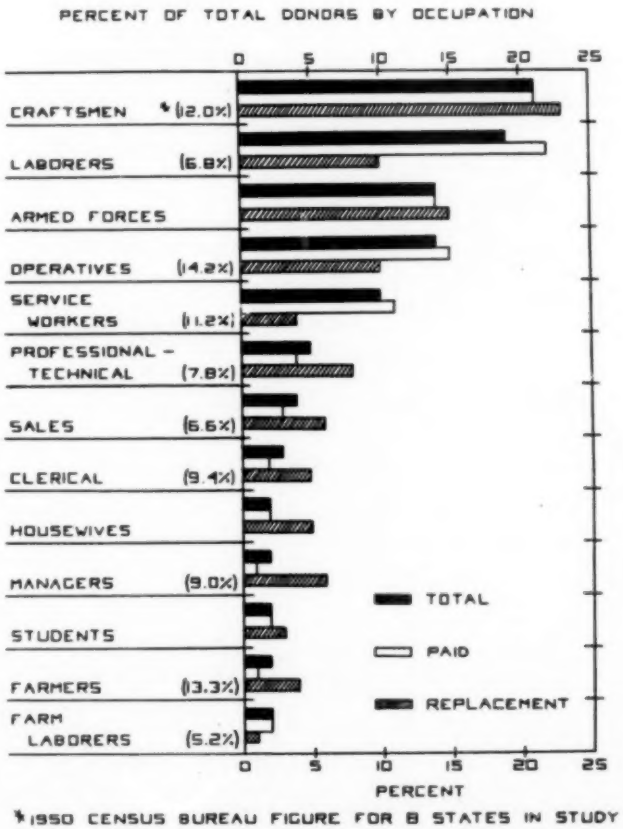

Fig. 1

While the majority of donors, both paid and replacement, come from middle income occupational groups, they donate blood in significantly larger numbers than would be expected, based on the proportion of the population which they represent, and 2) there are no that employment versus unemployment at the time of donation has a significant relationship as to whether an individual presents himself as a paid or a replacement donor. Nearly twice as many replacement donors were employed (89%) as were paid donors

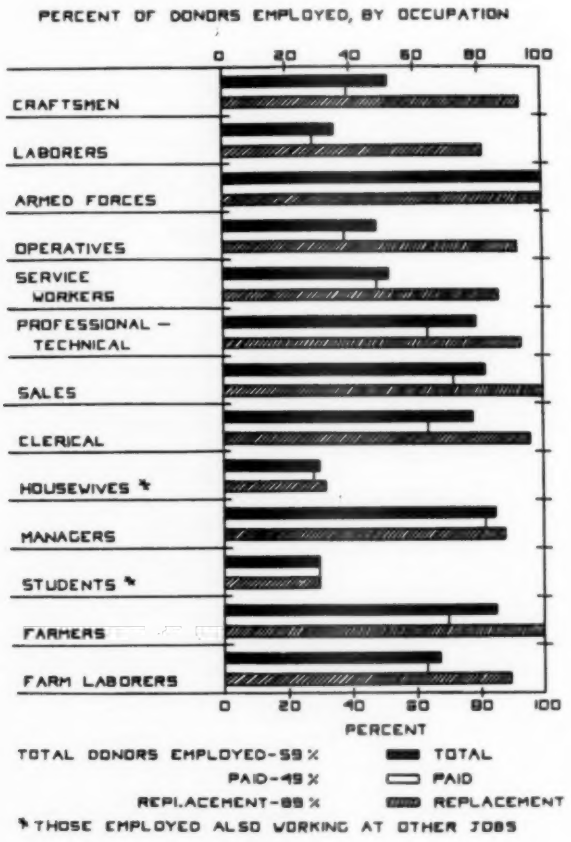

Fig. 2

real differences in the occupational status of the paid and replacement donor groups.

DONOR EMPLOYMENT. The size of the employed donor group within the total sample is sufficiently large (59%) to compare favorably with the 1957 employment status of the total labor group (95%). A study of Fig. 2 quickly shows (49%). Excluding the Armed Forces donors, who are all employed, the 4 occupational groups who provide most of the donors of both types were 88% employed at the time of donation when they gave as replacements, but only 39% were employed when they gave as paid donors.

It is of interest in this connection

that there are a very considerable number of these donors in both classifications who give repeatedly and do so over a long period of time. It is also known that many persons who are repeat donors give from time to time in both categories. The figures also suggest that an individual may be more likely to donate blood to help a friend or relative when he is employed, and perhaps also is more likely to be asked to do so. On the other hand, the total figure of 49% employment among paid donors would suggest that personal financial stability has no marked effect on the willingness of many individuals to donate blood for a fee. It is important in this regard to point out that we pay a relatively low fee to blood donors. Replacements "earn" a credit of $10.00 toward the total service charge to the patient of $20.00. Paid donors who are called in because we want their group and type of blood also receive a $10.00 fee, primarily because they respond when we need them. Donors who voluntarily present themselves in hopes that we need and can take them are paid a fee of $5.00.

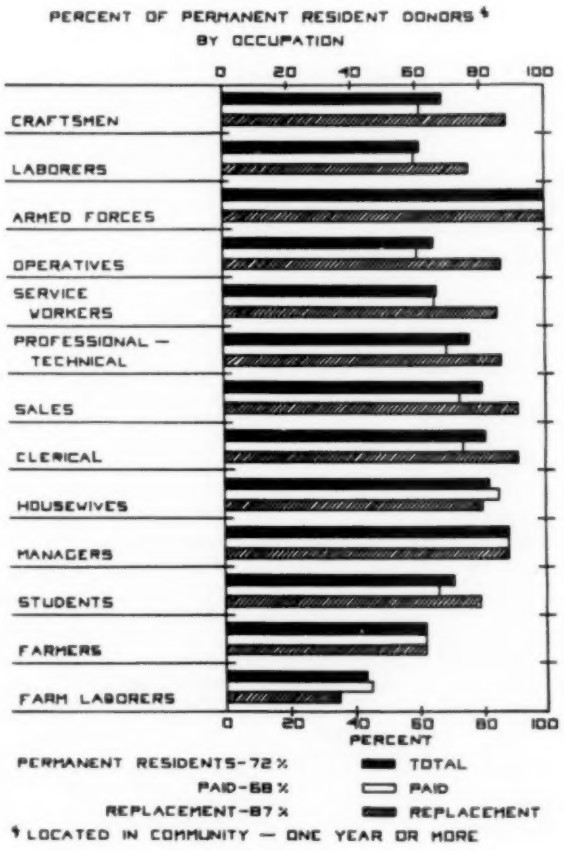

Fig. 3

PERMANENT RESIDENCE. It seems

quite significant that there is no striking difference between the 2 groups of donors in reference to their permanent residence in the area where they donate blood. As will be noted in Fig. 3, replacement donors, as would be expected, predominate slightly as 87% of replacements, the combined total of permanent residents being 72% of all donors. Thus the chances are that about 9 of 10 replacement donors will be permanent residents, and that somewhat fewer, or 7 of 10, will be residents in the paid-donor group.

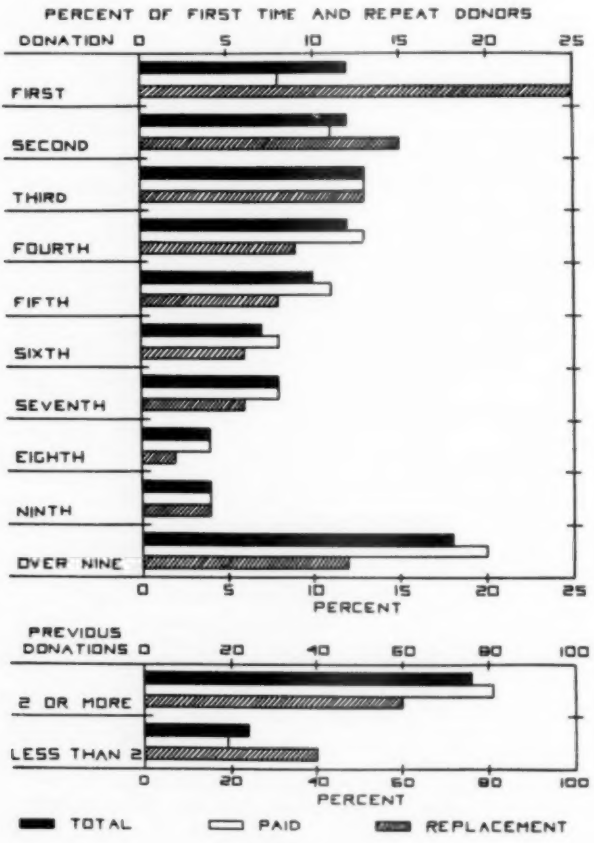

Fig. 4

permanent residents in all occupational groups, except for Managers and Farmers, where the division is equal. (Armed Forces donors were arbitrarily all considered to be residents of the community, for the reason given previously.) The total percentages for the 2 groups are 68% of paid donors and

Actually, it is rather striking that there is so little difference; and it does not support the opinion, which has often been voiced, that the paid donor is usually a transient and, therefore, by inference a somewhat unreliable or inferior type of person.

PREVIOUS DONATIONS. One of the

facets in which we were extremely interested was the determination of the number of previous donations among both groups of donors. We were aware that there were a large number of repeat donors who, therefore, were well known to us as reliable and whose blood we believed had been demonstrated as safe to use, because of our repeated experience with them. As shown in Fig. 4, the differences between the 2 groups are most striking. While only a total of 12% of all donors were giving for the first time, there were but 8% of the paid-donor group compared with 25% of the replacements. Among the repeat donors, it will be noted that there is but little difference between the 2 groups in those giving for the second through the ninth time, but that there is again a striking difference in the 18% of "long-time" donors who have given more than nine times. This group includes 20% of the paid donors, compared to only 12% of the replacements.

Actually, it is not surprising that the percentage of "new" replacement donors is relatively high. This finding, as well as the remainder of the data, lends support to our belief that the "willing" blood donor comprises a rather small percentage of the population, but that he is ready to serve whenever he is needed. The data also indicate that most of these individuals first donate as replacements and subsequently serve repeatedly, either as paid or replacement donors. It has also been observed that a significant number of "new" replacement donors almost never return. These are truly the "unwilling" donors who have been "forced" into giving blood by social pressures. Further substantiation for these opinions is found in the data in the lower part of Fig. 4. Seventy-six per cent of all donors have previously given 2 or more times; 81% of the paid-donor group, and a respectable 60% of the replacements. Thus, only 24% of our donor population have given blood less than 2 times, but the difference between the 2 groups is striking; there are only 19% of the paid group, as compared to 40% of the replacements. It should be noted here that the dividing point of 2 previous donations was selected because it relates to the criteria used for rejecting permanently donors who have been associated with cases of presumed transfusion-caused hepatitis. In cases following multiple-unit transfusions, it is believed that the biologic evidence of 2 or more previous "safe" donations is a most significant factor in justifying retention of the person as a blood donor (Alsever[1]).

MOTIVATION FOR FIRST DONATION. The reasons for the first blood donation are presented in Fig. 5. While 47% of all the donors first gave as replacements, there was a marked difference in the 2 groups. A striking total of 84% of those presenting themselves as replacement donors during the study had first given as replacements, compared to but 36% of the paid group; while 51% of those presenting themselves as paid donors had also given first for pay. It is also striking that, in the 40% giving as paid donors at the time of their first donation, there were only 4% who presented themselves as replacement donors in the study group. To present this in another way, while 47% of the total group were at first replacement donors, only 24% were giving as replacements during the study. Also, while but 40% of all donors gave the first time for pay, 76% were paid donors during the study. Only a very small percentage of donors made their first blood donation as military personnel for military use or as volunteers (not replacements) to Red Cross Regional Centers, 7% and

6% respectively, and there were essentially equal numbers of both the paid and replacement-donor groups.

PLACE OF FIRST DONATION. We were also interested in learning what percent of the donor population had been recruited or interested in becoming blood donors by our own blood bank system, as well as the numbers first recruited by others. As shown in Fig. 6, 46% of all donors made their first donation at Southwest Blood Banks, with but little difference in the percentages represented in the paid and replacement groups. Almost as many, 40%, had first donated in other independent blood banks, again with little difference between the 2 groups. However, our system had recruited a somewhat higher percentage of the paid-donor group and other blood banks a bit higher percentage of the replacement group. As in the case of the reason for the first donation, the numbers of donors giving first at military installations and Red Cross Centers are quite small, 11% and 3% respectively, with essentially no difference between the paid and replacement-donor groups. The apparent discrepancies between the percentages of donors giving for the first time at military or Red Cross Centers and those who gave the first time for local military or Red Cross use are due to the inevitable confusion connected with the multiple recruitment programs for military reserves of plasma or albumin, for local or overseas military uses, and for local Red Cross use, together with the fact that donors could often give at both types of blood centers, as well as at a number of independent blood banks, for more than one of these purposes.

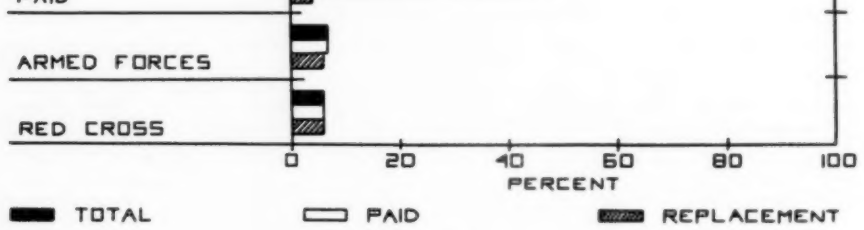

Fig. 5

USEFULNESS OF DONATION. As an ancillary part of this study, the questionnaire cards from which the preceding data were derived also showed the donor's blood unit number, so that laboratory data relating to use of the blood could be compared. Two interesting findings resulted. Positive serologies were found nearly twice as often in replacement donors. Of the 12,759 donors studied, there were 129 positive serologies, or 1.01%, which is consistent with our total donor experience. The 9,701 paid donors showed a rate

of 0.83%, with 81 positive serologies, while there were 48 positive serologies among the 3,058 replacement donors, a rate of 1.56%. Secondly, there were twice as many "short" (incomplete and unusable) units obtained from the replacement donors as from the paid-donor group, although there were 3 times as many paid donors drawn. The "short" unit is most commonly the result of anxiety and nervousness which produce fainting with a drop in blood pressure, venous collapse, and cessation of the flow of blood into the bottle. This further supports the observation that quite often the replacement donor is an "unwilling" donor who, therefore, is upset over the prospect of giving blood.

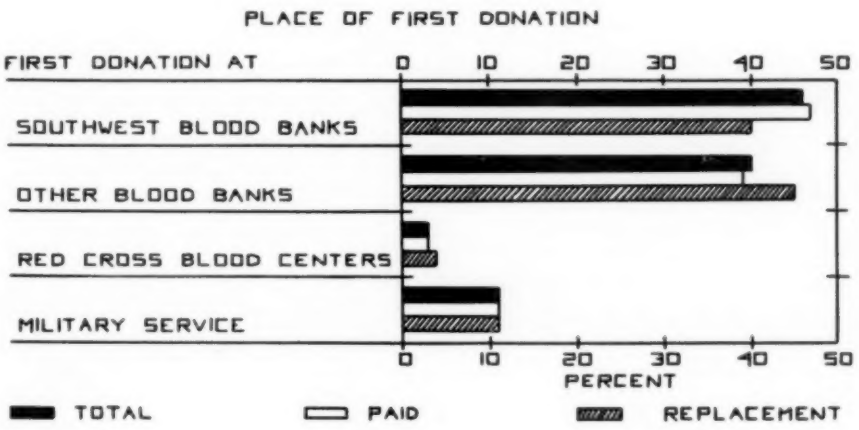

Fig. 6

Summary and Conclusions. Several characteristics of blood donors were studied in installations of Southwest Blood Banks in 12 cities in 8 states. A significant sampling of the total annual donor population was made by obtaining data from 12,759 unselected, consecutive blood donors during 5 seasonally spaced weeks of 1958. Seventy-six per cent were paid donors; 24% were replacements for specific patients.

In relation to the total donor group, 78% of donors are derived from only 5 of the occupational categories who represent about 48% of the employed population and are in the middle income brackets. They constitute the majority of both paid and replacement donors. While 59% of all donors were employed at the time of the donation under study, almost twice as many replacement donors (89%) were employed at the time as were paid donors (49%). Seventy-two per cent of all the donors were permanent residents of the community in which they gave blood; 87% of replacements (9 of 10) and 68% of paid donors (7 of 10). One out of every 4 replacement donors (25%) is giving blood for the first time, while this is true of only one out of every 12 paid donors (8%). The percentage of the 2 groups is about the same among those giving for the second to the ninth time, but paid donors with over nine donations considerably outnumber replacements. Seventy-six per cent of all donors had given more

than twice previously. This was true of 81% of the paid donors, compared to 60% of the replacements. Forty-seven per cent of all donors gave the first time as replacements, and 46% made their first donation to Southwest Blood Banks. Persons who are willing, regular and reliable blood donors comprise a relatively small percent of the population and respond repeatedly to need, both as paid and replacement donors.

The experience with and data concerning the paid-donor group and the replacement donors indicate therefore, that what differences there are show the paid donor to be a more valuable and reliable resource. There are no significant occupational differences. The paid donor is about twice as likely to be temporarily unemployed when he gives blood as is the replacement donor, but he is only slightly less likely to be a permanent resident. However, a much larger percentage of replacement donors are "new" than are paid donors, and 8 of 10 paid donors have given at least twice previously, compared to 6 of 10 replacement donors. Paid donors are significantly less likely to provide unsuitable units because of positive serologies and incompleted bleedings ("short" units). While there were many reliable repeat donors in both groups, there were no findings to justify any preference for the replacement donor over the paid donor; in fact, the reverse seems to be more generally true.

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SUMMARIO IN INTERLINGUA

Le Donator de Sanguine:
I. Qui es Nostre Donatores de Sanguine?
Un Analyse del Characteristicas Social e Altere de 12.759 Donatores de Sanguine

In bancas de sanguine in 12 citates de 8 statos del sud-west del Statos Unite, plure characteristicas del donatores de sanguine esseva studiate. Un proba significative del total population annual de donatores esseva effectuate per obtener datos ab 12.759 consecutive non-seligite donatores in le curso de 5 saisonalmente intervallate septimanas del anno 1958. Septanta-sex pro cento del donatores esseva donatores pagate. In 24% del casos il se tractava de offertas de sanguine de reimplaciamento pro patientes particular.

Septanta-octo pro cento del donatores del gruppo total veni de solmente 5 del categorias occupational. Istos representa 48% del population empleate e corresponde a nivellos intermediari de salario. Iste factos vale pro le donatores pagate e pro le offerentes de sanguine de reimplaciamento. Durante que 59% de omne le donatores esseva empleate al tempore del donation coperite per iste studio, quasi duo vices plus donatores de reimplaciamento (89%) esseva empleate a ille tempore que donatores pagate (49%). Septanta-duo pro cento de omne le donatores esseva residentes permanente del communitate ubi le sanguine esseva donate. Isto valeva pro 87% del donatores de reimplaciamento (9 ex 10) e pro 68% del donatores pagate (7 ex 10). Un ex omne 4 donatores de reimplacia-

mento (25%) offere sanguine pro le prime vice, sed isto vale pro solmente un ex omne 12 donatores pagate (8%). In le duo gruppos, quasi le mesme procentage de donatores face le secunde usque al none donation, sed donatores pagate con plus que novem donationes es considerabilemente plus numerose que donatores de reimplaciamento con plus que ille numero de donationes. Septanta-sex pro cento de omne le donatores ha historias de plus que duo previe donationes. Isto vale pro 81% del pagatos e 60% del reimplaciantes. In 47% de omne le casos, le prime donation esseva un donation de reimplaciamento. Subjectos qui ha le bon voluntate de facer donationes de sanguine e qui, como donatores, es regular e digne de confidentia representa un relativemente basse procentage del population. Illes responde repetitemente al demanda pro donationes de sanguine, tanto como donatores pagate como etiam como donatores de reimplaciamento.

Le experientia con respecto al donatores pagate e etiam le datos colligite con respecto a illes indica que, in tanto que illes differe ab le gruppo de donatores de reimplaciamento, illes es un fonte plus preciose e plus digne de confidentia in le provision de donationes de sanguine. Il non existe ulle significative differentias occupational. In le caso del donator pagate il es circa duo vices plus probabile que ille se trova sin empleo al tempore del donation que in le caso del donator de reimplaciamento, sed il es solmente levemente minus probabile que le donator pagate es un residente permanente del communitate. Tamen, un multo plus alte procentage de donatores de reimplaciamento es "nove" donatores. Octo ex 10 donatores pagate ha facite al minus duo previe donationes, sed isto vale pro solmente 6 ex 10 donatores de reimplaciamento. In le caso de donatores pagate il es significativemente minus probabile que le donation es inacceptabile a causa de positive tests de serologia o a causa del non completion del sanguinamento. Durante que donatores digne de confidentia esseva numerose in ambe gruppos, nulle observation justificava preferer le donator de reimplaciamento al donator pagate. De facto, le contrario pareva valer a generalmente parlar.

THE BLOOD DONOR
II. BLOOD DONORS ASSOCIATED WITH HOMOLOGOUS SERUM HEPATITIS: AN ANALYSIS OF 211 DONORS INVOLVED IN 70 CASES

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THE accidental transmission of homologous serum hepatitis is generally considered to be one of the most important problems in blood transfusion therapy today. No laboratory test is known which will detect donors who are carriers of the virus. A donor's history cannot be relied upon to exclude carriers, partly because of possible willful concealment or poor memory, but principally because most are innocent carriers who have never had a clinically diagnosable illness. The disease in the patient is impossible of positive etiological determination; first, because of its long incubation period, perhaps as short as 40 days and up to 180 days; second, because of the several ways in which the virus can be introduced parenterally; and third, because of the close clinical similarity to, and the apparently overlapping incubation period of, the endemic infectious type of viral hepatitis. Finally, it is worthy of note that lawsuits are being brought with increasing frequency because of damages due to alleged transfusion-caused viral hepatitis. These problems have been dealt with in detail in a previous paper (Alsever[2], Editorial[3]).

Having recently completed a study of certain characteristics of a blood donor population (Korzekwa, Jordan and Alsever[5]), it became of interest to determine whether there might be any significant differences between the donors who are involved in cases of presumed transfusion-caused hepatitis and the donor group as a whole. This interest was stimulated greatly by 2 reports which suggested that carriers of the virus were more common among paid donors than replacement or so-called volunteer donors. Kunin[6] reported on the incidence of hepatitis in patients receiving blood from each of 5 sources supplying two Veterans Administration hospitals in the Boston area. Blood received from one commercial blood bank was responsible for a significantly higher incidence of the disease, attributable presumably either to poor donor screening techniques, a high carrier rate in the donor population, or both.

The other report was made by Allen *et al.*[1], in a study of the incidence of hepatitis and type of donor blood used in a randomly selected series of 1,894 patients who were observed for a 6-month follow-up period from 1947 to 1957 at the University of Chicago Clinics. Of 44 cases of presumed transfusion-caused hepatitis, 8 occurred in 1,152 patients receiving blood only from family-recruited donors (a 0.69% case rate), 13 were in 311 patients receiving only paid-donor blood (a 4.13% case rate), and 23 in 431 patients receiving both types of donor blood (a 5.3% case rate). Considering the single-unit transfusions only, there were 569 followed recipients with 2 cases of hepatitis (a rate of 0.3%) among patients receiving only "family" donor blood, and 186 followed recipients with 6 cases of hepatitis (a rate of 3.2%) among those

receiving only paid-donor blood. An average of 3.4 units per patient was used. A total of 42,407 bloods were employed during the 10 years for a total of 12,598 patient-transfusion episodes (blood only); 31.7% of these units were from paid donors. Allen concluded that the observed case rate of transfusion hepatitis was 7 to 10 times as high when paid donors were used instead of those recruited by the family. As will be shown, our findings lead to a considerably different conclusion. We are impressed that Allen's data may well not have been truly representative of the experience of the total group of 12,598 transfused patients. For example, during the 10-year period 31.7% of the blood was from paid donors but only 16.4% of the followed cases received only paid-donor blood, while the number of cases receiving only family-recruited donor blood is much larger in relation to the total per cent of family donors. This small group of paid-donor cases could have by chance included most of the hepatitis cases in this group. In addition, comparison of the yearly data does not indicate that the case rate rose in proportion to the increase in the percentage of paid donors used. The average paid-donor use for the years 1950-53 is 30.6% and the case rate per donor is 0.32%, while 60.6% paid donors were used in the years 1954-57 with an almost identical donor case rate of 0.38%. One is impressed that 2 other factors may have had an important bearing on the rising case rate observed over the 10-year period; first, an increasing awareness of the disease and its relationship to the transfusion of blood; and second, a coincidental increase in the carrier rate among blood donors in the Chicago area.

Material. The study material comprises data accumulated during a period of about 3 years, from October, 1956, to July, 1959. As will be noted in Table 1, a total of 375,744 blood donations were used as whole blood. Since many of these persons are repeat donors, this does not represent that many different individuals. Sixty-one per cent of these were paid donors and 39% were replacing for patients. There were a total of 70 cases* of pre-

TABLE 1.—A. TOTAL DONORS vs. INVOLVED DONORS

All Donors	*Number*	*%*	*Involved*	*%*
Paid	244,825	61	141	67
Replacement	159,201	39	70	33
Total	404,026	100	211	100

B. DONOR (UNIT) INVOLVEMENT RATE

*Bloods Used**	*Involved Donors*	*Rate*
375,744	211	0.56% / 1 in 1780

*93% of total units drawn were used as whole blood.

C. HEPATITIS CASE RATE

*Average** *Blood Use*	*Estimated Cases Transfused*	*Hepatitis Cases*	*Case Rate*
2.49	150,901	70	0.046% / 1 in 2155

*Per patient transfused.

sumed transfusion-caused serum hepatitis during this period of time in patients receiving only whole blood. Two hundred eleven individual blood donors were involved, 67% of whom were paid and 33% were replacements. Thus, there was no significant difference from the ratio present in the total group of donors. In reviewing the characteristics of this group of 211 donors, the significant information in regard to the donations in question was whether the donation was made by a paid or a replacement donor, how many previous blood donations he had on record with us, and the fact that there was a completely neg-

*These were voluntarily reported within the areas served by the Southwest Blood Banks system of 20 blood bank installations in 10 states. The diagnosis was verified by a physician's case report showing typical history, symptoms, physical signs, and clinical laboratory findings.

ative history regarding previous viral hepatitis or recent exposure to this disease. In most instances the donors were available and reported for confirmatory re-examination. To date, there have been no instances where the same individual was involved in 2 cases. In fact, the policy employed for reviewing and rejecting such "suspect" donors largely precludes this possibility. It is discussed in detail in another paper (Alsever[2], Editorial[3]). It will be noted that the involved donors occurred at the rate of 0.056%, or 1 in 1780 donors, among the units used as whole blood. The recipient case rate was 0.046%, based on studies showing that the average use of blood in the area served is 2.49 units per patient. This case rate is comparable to the rate of 0.06%, found by Maxwell[7], in a study of the incidence of transfusion hepatitis, based on the voluntary reporting of serum hepatitis to the Milwaukee Blood Center in a group of some 9,500 transfused patients.

Results. ANALYSIS OF HEPATITIS CASES. The basic data concerning the donors associated with each of the 70 cases are detailed in Table 2. Cases are separated into 3 groups according to the source of the blood, each group is listed in order according to the number of units used, and the paid or replacement status with the previous donor experience for each unit is indicated. Table 2-*A* shows the data for the 27 cases receiving only paid-donor blood; Table 2-*B*, that for the 11 cases receiving only replacement-donor blood; and Table 2-*C*, the data for the 32 cases receiving both types of donor blood.

It is of interest to compare the use of blood in these cases with an analysis of a much larger group of transfused patients. Among the 70 patients acquiring hepatitis, 33% received only a single unit of blood. Many of these very possibly were unnecessary transfusions. Only 16% of the cases were in patients receiving 5 or more units of blood. Data for the larger group of cases show that about 25% of patients received only one unit, and that 22% received 5 or more. These figures were obtained concurrently from analysis of a series of 1,297 patients in Phoenix who received 4,297 units of blood, an average use of 2.49 units.

CAUSATIVE RELATIONSHIP OF PAID AND REPLACEMENT DONORS. Inspection of Table 3 clearly shows that the reported cases of hepatitis presumably due to the blood of paid or replacement donors divide very nearly in proportion to the total number of paid and replacement donors involved. Of the 70 cases, 27 (38.6%) received all paid-donor blood, 11 (15.7%) all replace-

TABLE 2.—ANALYSIS OF DONOR RECORDS BY CASES

A. CASES RECEIVING ONLY PAID DONOR BLOOD

Case Number	*Number of Donors*	*Donor Experience (Previous Donations)* None	1	2	or More
1 through 17	Single Unit Transfusions	4	6	1(2)	5(3) 1(6)
18	2	2			
19	2		1		1(3)
20	2	1			1(3)
21	2	2			
22	2		2		
23	3	1		1(2)	1(4)
24	3		1		1(3) 1(6)
25	4	2	1	1(2)	
26	7	2	2	2(2)	1(3)
27	8	3	3	2(2)	
27 Cases	52	17	16	19	

TABLE 2.—*B*. CASES RECEIVING ONLY REPLACEMENT DONOR BLOOD

Case Number	*Number of Donors*	*Donor Experience (Previous Donations)* None	1	2 or More
1 through 6	Single Unit Transfusions	2	3	1(2)
7	2	2		
8	2	1	1	
9	2		2	
10	3	2	1	
11	3		3	
11 Cases	18	7	10	1

TABLE 2.—C. CASES RECEIVING BOTH PAID AND REPLACEMENT DONOR BLOOD

Case Number	Number of Donors	Donor Experience (Previous Donations)					
		None		1		2 or More*	
		P	R	P	R	P	R
1	2		1			1(3)	
2	2	1	1				
3	2				1	1(2)	
4	2			1	1		
5	2		1	1			
6	2		1			1(3)	
7	3		1	1		1(2)	
8	3		1	1		1(2)	
9	3	1	1			1(2)	
10	3	1				1(5)	1(6)
11	3		1	1		1(4)	
12	3	1	1				1(2)
13	3			2	1		
14	3	1	1			1(2)	
15	4		1	1		2(2,3)	
16	4	2	2				
17	4	1	2	1			
18	4	1	2			1(4)	
19	4	1	1			2(3,10)	
20	4	2	1			1(13)	
21	4	2			1	1(5)	
22	4	2			1	1(2)	
23	4	1	2		1		
24	5			2		1(2)	2(2,3)
25	5	2	2			1(3)	
26	5		2	2		1(4)	
27	5	3				1(2)	1(2)
28	6		1	2		3(2,5,8)	
29	6			3	1	2(4,5)	
30	8	3	1			4(3,4,7,13)	
31	14	1	8	2	1	2(2,4)	
32	15	2	4	4		5(2,3,4,9,13)	
32 Cases	141	28	39	24	8	37	5
		67		32		42	

P—Paid
R—Replacement
*Figures in parentheses indicate the number of previous donations for the donors shown: that is, 5(3) indicates 5 donors with 3 previous donations.

ment blood, and 32 (45.7%) received both types. The relationship of the first 2 groups of cases, 38.6% in the paid-donor group to 15.7% in the replacement group, is essentially similar to the relationship of the 2 groups of donors, 67% paid and 33% replacement. This suggests that the carrier rate is about the same for both groups. If it is assumed that this is true, then one would have expected 25.5 cases instead of 27 due to the paid donor, and 12.5 instead of 11 due to the replacement, based on the 67% to 33% ratio of the

211 donors involved. It should also be noted that the donor ratio in the above group of cases shows no essential difference from the ratio of 61% paid to 39% replacement in the total group of donors during the 3-year period. Therefore, the case distribution to be expected if the carrier rate in paid and replacement donors is essentially the same is not significantly different from what actually occurred.

TABLE 3.—ANALYSIS OF CASES BY PAID STATUS OF DONORS USED

Type of Donors Used	*Number of Cases*	*%*	*Adjusted Number Cases*	*%*	*% Involved Donors*	*% Total Donors*
All Paid	27	38.6	48	68.6	67	61
All Replacement	11	15.7	22	31.4	33	39
Both	32*	45.7				
Total	70					

*Total of 211 donors; 141 paid (67%), 70 replacement (33%). The 32 cases thus divide: 21 presumed paid, 11 replacement.

Because of the close similarity of the ratio of involved donors to the ratio of the 38 cases receiving only one or the other type of blood, it seemed reasonable to attribute the causative donor type in the 32 cases receiving both types of blood on the same basis. Thus, 67%, or 21 cases, are probably due to paid donors and 11 cases (33%) are probably due to replacement donors who presumably are virus carriers. This allocation results in 68.6% of the cases (48) being attributable to the 67% of paid donors and 31.4% of the cases (22) attributable to the 33% of replacement donors. Actually, in the involved group of 211 donors there were 6% fewer paid donors and 6% more replacements than there should have been in comparison to the entire donor population. If both groups have an equal carrier rate, the expected cases from all blood used then would have been 47 from paid donors instead of 48, and 23 from replacements instead of 22. The differences noted do not appear to justify any conclusion other than the following: the hepatitis virus carrier state appears to occur at an approximately equal rate among both paid and replacement donors.

CAUSATIVE RELATIONSHIP OF FIRST AND SECOND-TIME DONORS. There is, however, a very striking common characteristic of most of the 211 donors, and this differs significantly from what is found in the total donor group. From Table 4, it will be seen that 43 of the 70 cases (61.4%) received at least one unit of blood from "new" (first-time) donors and 19 additional (27.1%) received no "new" donor blood but had at least one unit from second-time donors (one previous donation), making a total of 88.5% of the cases who received blood with which there had been either no previous experience, or but one previous use in patients (a single biologic trial). This observation would suggest that the causative relationship of the blood should be seriously questioned in the group of 8 cases involving only donors whose blood had been used previously two or more times in patients who suffered no ill effects. The donor-use experience in these 8 cases all single-unit transfusions, was: 2 donors, 2 prior units; 5 donors, 3 prior units; and 1 donor, 6 prior units.

It will also be noted that, of the 211

involved donors, there were 43.1% "new" donors and 27.5% second-time donors, as compared with 12% and 12% respectively in the total donor population, and that the incidence of donors with 2 or more previous donations was but 29.4% compared with 76% among the total donors (Korzekwa, Jordan and Alsever[5]).

TABLE 4.—ANALYSIS OF CASES BY PREVIOUS EXPERIENCE OF DONORS USED

"Experience" of Donors Used	*Number of Cases**	*% of Cases*	*% of Involved Donors*	*% of Total Donors*
"New" Donors	43	61.4	43.1	12
One Previous Donation	19	27.1	27.5	12
Two or More	8	11.5	29.4	76

*Cases grouped according to the donor with least "experience" among the blood units given.

This significantly implicates the biologically untested donor as a chief source of the virus carrier. It supports entirely our policy, in reported hepatitis cases following multiple-unit transfusion, of requiring at least 2 previous donations with no evidence of hepatitis in the recipients during the period of 6 to 18 months prior to the case in question to justify the retention of a suspect donor in the active donor files (donors in single-unit cases are arbitrarily rejected) (Alsever[2]).

These data emphasize the dilemma of the blood banks, since an adequate donor supply cannot be maintained without recruiting and using new donors constantly; yet they evidently are the most dangerous group, for they include the great majority of the virus carriers, and there is no means of identifying which of them should not be used. Thus, the need for a specific screen test which is usable by a blood bank becomes even more significant, because the primary effort can most productively be devoted to a donor group which can be easily segregated and specially studied. It would seem almost certain that a specific test method would have to be based on the immunologic response to the presence of the hepatitis virus in the body. Regrettably, until such a test is available, we are forced to rely on the unhappy results of biologic trial in patients or in volunteers to identify donors who may be virus carriers.

PREDOMINANCE OF "NEW" AND "ONE-TIME" DONORS. There are a number of details regarding this finding that are of interest and merit brief discussion. Further analysis of the 70 cases shows that the significance of the "new" and the "one-time" donor is consistent in all 3 groups of cases; such blood was given in 74% of the 27 cases receiving only paid-donor blood, in 91% of the 11 receiving only replacement-donor blood, and in 100% of the 32 cases receiving both types of donor blood. In the latter case group, there were 28 "new" paid donors plus 39 "new" replacements, and 24 "one-time" paid donors plus 8 "one-time" replacements, totalling 99 (70%) of the 141 donors involved. Only 3 of the 32 cases received this kind of blood from paid donors only, and 3 more from replacements only. "New" and "one-time" donors of both groups were involved in the remaining 26 cases. Finally, if one segregates those cases in the 2 groups who were transfused entirely with either replacement or paid-donor blood which was all "new" donor blood, all "one-time" donor blood, or all both "new" and "one-time" donor blood, the same predominance of cases prevails, but it is very striking in the use of replacement donors. Such cases constitute almost all, 91%, of the replacement-donor-only cases, and but 55.5% of the paid-donor-only group.

The average donor exposure in each of the 3 groups is also of interest. The entire group of 70 cases had a higher donor exposure rate (3.01) than the average figure of 2.49. However, the exposure rates of the paid-only and replacement-only groups were somewhat lower than the average (1.95 and 1.63, respectively), while the rate was considerably higher (4.40) in the 45.7% of the cases receiving both types of donor blood.

56 of the paid donors (40%) and but 6 replacements (8%), while there are 81% "experienced" among paid and 60% among replacement donors in the total donor group. This evidence, together with that in the preceding paragraph, suggests that the "new" or "one-time" replacement donor appears to be relatively more frequently involved than his paid counterpart.

RELATONSHIP TO THE THYMOL TURBIDITY TEST VALUES. Fourteen of the 70

TABLE 5.—ANALYSIS OF INVOLVED DONORS BY PAST DONOR EXPERIENCE

Number Previous Donations	*Paid Donors*	*%*	*%* Total Paid Donors*	*Repl. Donors*	*%*	*%* Total Replace. Donors*	*All Donors*	*%*	*%* Total Donors*
None	45	32	8	46	66	25	91	43	12
1	40	28	11	18	26	15	58	28	12
2	19			4			23		
3	16			1			17		
4	8			0			8		
5	4			0			4		
6	2	37	61		8	48		27	58
7	1			0			3		
8	1			0			1		
9	1			0			1		
More Than 9	4	3	20	0	0	12	1 4	2	18

*Figures for total annual donations.

The "new" and "one-time" donors predominate not only in terms of the number of cases in which their blood was used, but also in absolute percentages of the entire group of 211 involved donors, as shown in Table 5. The differences between this group and the total donor population are striking in entirety, and most marked percentage-wise in the replacement-donor group, although it is numerically smaller. The "new" and "one-time" donors total 85 (60%) of 141 paid donors and 64 (92%) of 70 replacements, while the percentages of these groups in the total donor population are but 19% "new" and "one-time" among paid donors and 40% among replacements. In contrast, the "experienced" involved donors total

reported cases occurred in the Phoenix area, where a study is currently in progress to evaluate the thymol turbidity test as a donor screening technique in accordance with the method of Jennings *et al.*[4], in which a screening level of 8 Shank-Hoagland units is used. These 14 cases are identified in Table 2 as follows: in 2-*A* (paid donors only), cases 19, 20, and 27; in 2-*B* (replacement donors only), cases 6 and 10; in 2-*C* (both types of donor), cases 4, 12, 14, 16, 21, 22, 23, 27, and 29. Analyzing these data as was done in Tables 3 and 4 for all cases, but now relating the findings to the blood unit thymol values as well, one observes the following.

Fifty-one donors were involved, 34

paid (67%) and 17 replacements (33%); the same ratio as that in the total group of 211 involved donors. The 5 cases attributable solely to the paid donor and to the replacement donor (3 and 2, or 60% and 40%, respectively) themselves conform closely to the ratio of the two groups in the total of 51 donors. When the remaining 9 cases are distributed on the same basis, there is a total of 9 cases attributable to the paid donor (64.7%) and 5 to the replacement (35.7%). This compares favorably with the ratio of 67% to 33% in the group of 51 donors.

Only 5 cases (35%) received one or more units of "high" thymol blood. Seven "high" units* were involved; 5 were among the 34 paid donors (an incidence of 14.7%) and 2 were among the 17 replacements (11.7% incidence). However, 24 "new" donors and 14 "one-time" donors are involved, the former in 10 cases (71%) and only the latter in 3 additional (21%), a striking total for both of 92% of the 14 cases. As before, the per cent of these 2 groups of donors in the 51 involved (74.5%) far exceeds expectancy (24% of all donors).

Although it is appreciated that no significant conclusions can be drawn from these few cases, the marked difference between the association of "high" thymol blood and blood from "new" and "one-time" donors with these cases cannot be ignored. In relation to the thymol screening value, 75.0% of the 44 normal-thymol donors and 71.4% of the 7 with "high" thymol were without "experience." Furthermore, one or more such donor was also involved in all but one of the 5 "high-thymol" cases. On the basis of these 14 cases, the correlation of lack of "experience" appears to be of far more significance than is a high thymol value of the donor bloods used, and it is quite comparable to the findings in the total group of 70 cases.

As a preliminary evaluation of the thymol turbidity screening test for donors, the study results obtained thus far are as follows. The incidence of "high" thymol values in all the blood processed is 5%. There have been a total of 14 cases of hepatitis. Of these, 5 cases have occurred in 297 patients receiving some "high" thymol blood who have been followed for 6 to 12 months after transfusion, a case rate of 1.68%. In 435 similarly followed control cases, selected at random, there have been 4 cases, a rate of 0.92%. The remaining 5 reported cases occurred in patients not selected for follow-up, but they were all in patients who received only normal-thymol bloods. Additional data are being accumulated and will be published at a later date.

Summary and Conclusions. A review of the previous donor experience in a group of 141 paid donors and 70 replacement donors who were involved in 70 cases of presumed transfusion-caused serum hepatitis shows that the 2 groups appear to be responsible as carriers in almost exactly the same ratio as each has to the total of 211 donors. Thus, the carrier rate evidently is essentially the same in both groups. However, it is strikingly evident that "new" donors and "one-time" donors are primarily implicated as carriers. Together, they are involved in 88.5% of the 70 cases, and their frequency in the group of involved donors is 3 times higher than in the total donor group. Cases receiving at least one unit of blood from "new" donors total 43, or

*The cases and donors involved are as follows: in Table 2-*A*, case 20, one donor (3-prior donations), case 27, 3 donors (2 "new" and one 2-prior donations); in Table 2-*B*, case 6, one donor (2-prior donations); and in Table 2-*C*, case 9, one donor ("new"), and case 21, one donor ("new").

61.4%; and there are an additional 19 cases, or 27.1%, who received no "new" donor blood but at least one unit from donors who had given only once previously. The replacement donor is relatively more significantly involved in these cases than is the paid donor; "inexperienced" donors make up 92% of the replacement group and 60% of the paid-donor group. Thymol turbidity test values were done in 14 of the cases. Although the number of cases is too few for valid conclusions, a "high" thymol value appears to have very poor correlation with the carrier state, while the lack of donor "experience" is again most striking.

These data clearly identify the group of blood donors who are most dangerous as potential carriers; they consist almost entirely of those donors with no previous experience or but one previous donation. This highlights the seriousness of the hepatitis carrier problem for blood banks, who could not continue to give service without constantly recruiting and using new donors. On the other hand, it would seem to make the problem somewhat easier when a specific test method is devised, since the effort in special screening can be concentrated largely in a relatively small group of donors with a very high rate of effectiveness. Finally, the data validate the previously published criteria, based on medicolegal considerations, for exclusion of suspect donors in cases following multiple-unit transfusions unless they have a record of 2 "safe" previous donations, in addition to other negative findings.

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SUMMARIO IN INTERLINGUA

Le Donator de Sanguine
II. Donatores de Sanguine Associate con Hepatitis del Typo Serohomologe Analyse de 211 Donatores Interessate in 70 Casos

Un revista del previe experientias donatori de 141 donatores pagate e 70 donatores de reimplaciamento qui esseva interessate in 70 casos de presumptive hepatitis seral del typo transfusionogene revela que le duo gruppos es responsabile como portatores in quasi exactemente le mesme proportion relative. Tamen, il es frappantemente evidente que "nove" donatores e donatores de un sol donation "sporadic" es primarimente implicate como portatores. Iste duo categorias de donatores es implicate, insimul, in 88,5% del 70 casos, e le procentage que illes representa in le donatores associate con casos de hepatitis es 3 vices plus alte que le procentage que illes representa in le gruppo total de donatores. Quarantatres del 70 patientes con hepatitis de typo serohomologe (61,4%) ha recipite al minus un donation de sanguine ab "nove" donatores, e 19 alteres (27,1%)—ben

que illes recipeva nulle sanguine ab "nove" donatores—recipeva al minus un donation ab donatores qui habeva facite solmente un previe donation. Le donator de reimplaciamento es relativemente plus significativemente implicate in iste casos que le donator pagate. Donatores "inexperte" representa 92% del donatores de reimplaciamento e 60% del donatores pagate. Tests de turbiditate a thymol esseva effectuate in 14 del casos. Le numero del casos non suffice a supportar conclusiones solide, sed il pare que un "alte" valor thymolic es mal correlationate con le characteristico del portator, sed le absentia de experientia como donator es de novo multo frappante.

Le datos identifica nettemente le gruppo de donatores de sanguine qui es le plus periculose como portatores potential. Illo consiste quasi completemente de donatores sin previe experientia o con non plus que un sol previe donation. Isto sublinea le gravitate del problema del portator de hepatitis ab le puncto de vista del bancas de sanguine que non poterea continuar lor servicio sin continuemente recrutar e usar nove donatores. Del altere latere, le situation simplifica le problema del test pro le detection de portatores, proque le effortio de organisar un test de detection pote concentrar se in grande mesura in un relativemente micre gruppo de donatores e nonobstante promitter un alte grado de efficacia. Finalmente, le datos confirma le validitate del previemente publicate criterios a base de considerationes medico-legal pro le exclusion de suspecte donatores in casos de hepatitis a transfusion multiple. Iste criterios demanda, a parte le negativitate de varie altere aspectos, un historia de al minus duo previe donationes a bon successo.

DEXAMETHASONE THERAPY WITH GASTRIC FUNCTION STUDIES IN PATIENTS WITH RHEUMATOID ARTHRITIS

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In 1957 a new family of anti-inflammatory steroids was synthesized containing in common a methyl grouping at the sixteenth carbon position (Arth *et al.*[1]). One of these, 9-alpha-fluoro-16-alpha-methyl-prednisolone, or dexamethasone, has received the most attention (Boland[2], Bunim *et al.*[3]). It differs chemically from triamcinolone by having a methyl instead of hydroxyl grouping at the 16 alpha carbon position.

Animal experimentation with dexamethasone revealed that its anti-inflammatory potency as gauged by granuloma inhibition was 190 times greater than hydrocortisone, and glycogen deposition 17 times that of hydrocortisone (Arth *et al.*[1]). Other studies (Arth *et al.*[1]) in rats revealed that dexamethasone as compared to hydrocortisone was 700 times as potent in inducing adrenal atrophy, 400 times greater in producing involution of the thymus, and 100 times more powerful in causing body weight loss. In adrenalectomized rats dexamethasone produced neither sodium retention nor potassium loss.

Preliminary clinical observations by other investigators (Boland[2], Bunim *et al.*[3]) indicate that dexamethasone is the most potent anti-rheumatic steroid thus far synthesized. Our experiences with the oral administration of dexamethasone* to 54 patients with rheumatoid arthritis are reported.

Procedure. More than half the patients were studied for 6 months or more, with only 7 under observation for less than one month. The method of administering dexamethasone was similar to that employed for other anti-inflammatory steroids, that is, an initial suppressive daily dose of 2 to 3 mg. was administered for 5 to 14 days after which the dose was gradually reduced to maintenance levels. Those individuals receiving other steroids were switched to estimated equivalent doses of dexamethasone and maintenance levels attained as before. Thirty patients had been taking triamcinolone prior to the administration of dexamethasone, 4 patients had received prednisone, and 20 had not received any steroid. Other therapeutic measures were continued without alteration. Half of the patients were simultaneously treated with gold salts, and practically all were taking salicylates in doses of 2 to 4 gm. daily.

At each visit the patients' joints were evaluated subjectively for pain, stiffness, and range of motion, and objectively for the degree of synovitis as demonstrated by the

*Merck Sharp & Dohme supplied the dexamethasone for this study.

amount of heat, swelling, fluid, tenderness, capsular thickening, and range of motion. A composite estimate of these findings was recorded in percentage, with 100% indicating maximum improvement. Clinical evidence of toxicity was sought at each visit. Observations were made for moon facies, hirsutism, ecchymoses, blood pressure changes, body weight, edema, and gastrointestinal disturbances. Other possible complications were also recorded. Laboratory procedures included urinalyses, blood counts, and sedimentation rates (Westergren), the latter at least once monthly and more frequently when the patient was first placed on the new medication. Blood sugars and electrolyte determinations for sodium, potassium, and chloride were done throughout the study. Approximately half the blood sugars were fasting and half, 2 hour post-prandial specimens. Serial gastric analyses were performed according to the technique of Kirsner and Ford[4]. These were done on 14 patients over an 8-month period of therapy; 9 of these were females. Histalog in a dose of 0.5 mg. per kg. body weight was used to stimulate gastric secretion. Eight specimens of gastric juice were obtained at 15-minute intervals, 4 before histalog stimulation, and 4 afterwards. The pH of each specimen was determined to insure the proper placement of the gastric tube. Volume, concentration in clinical units of free acidity, and mg. of hydrochloric acid were determined for each specimen. There were 34 gastric analyses. Controls were obtained in 11 individuals, 2 of which were done during a period when steroids were not given; 9 were performed during previous triamcinolone administration. The latter were considered controls since triamcinolone caused no significant change in gastric secretion in these patients (Zuckner *et al.*[5]). Roentgenograms of the upper gastrointestinal tract were done in 25 patients, most of whom had been receiving 1.5 to 2.0 mg. of dexamethasone daily for 6 months.

Results. The anti-inflammatory response to dexamethasone was very satisfactory. All but 3 patients demonstrated significant improvement (that is, greater than 50%). The alleviation of rheumatic manifestations was similar to that observed with other steroids as regards rapidity, degree, and duration of improvement. Relapse was also comparable to other steroids when the drug was discontinued. Three patients very decidedly preferred triamcinolone over dexamethasone for relieving rheumatic symptoms. The reverse was true in one individual. Several others showed only minor preferences for one preparation or the other, but the significance of this preference was difficult to assess.

The average daily maintenance dose of dexamethasone was 1.6 mg.; this was 20% of the maintenance level of triamcinolone.

TABLE 1.—EFFECTS OF DEXAMETHASONE THERAPY IN 54 PATIENTS WITH RHEUMATOID ARTHRITIS

Effect	*Number of Patients*
Weight gain	40
Moon facies	26
Increased appetite	25
Pyrosis, eructation, nausea	15
Ecchymoses	14
Edema	9
Bloating	8
Hirsutism	7
Peptic ulcer	4
Diabetes	2
Glossitis	2
Acne	2
Headache	1
Erythema	1

Leukocytosis and diminution in the sedimentation rate occurred with approximately the same frequency and to the same degree as with other steroids. Urinalyses revealed no abnormality except in one patient who developed glycosuria on a daily maintenance dose of 1.5 mg., but did not spill sugar while taking 10 mg. of triamcinolone daily. The fasting blood sugar was also elevated during dexamethasone therapy in this patient. A 2-hour post-prandial sugar was high in another individual whose daily dose of dexamethasone was 1.5 mg. The latter had a similar elevation while on triamcinolone therapy. Fifty-one other

TABLE 2.—RESULTS OF GASTRIC ANALYSES DURING DEXAMETHASONE THERAPY IN PATIENTS WTH RHEUMATOID ARTHRITIS

Patient	Sex	Age	Date	Drug*	Average Total Daily Dose (mg.)	Duration of Therapy (days)	Basal†			Histalog†		
							Vol. (ml.)	Cl.U.§	Output‡ (mg.)	Vol. (ml.)	Cl.U.§	Output‡ (mg.)
1. C.H.	F	63	4/1/57	Pred	12.5	150	39	17	24	77	56	158
			4/16/57	Tdac	12	8	52	40	76	51	92	335
			5/7/57	Tdac	10	21	50	24	15.9	83	89	150
			6/18/57	TOH	10	7	25	8.5	4.0	61	63	83
			11/25/58	D	1.75	179	57	15	35	99	76	315
			1/7/59	D	1.75	222	23	32	24	138	85	495
2. J.G.	F	43	11/22/58	D	2	20	20	14	54	98	108	403
			1/13/59	D	1.25	52	61	32	63	190	117	797
			3/24/59	D	0.5	70	29	3	00.3	61	145,	300
3. E.A.	F	57	1/13/59	D	2.0	72	15	18	10	34	15	19
			3/31/59	D	1.5	77	12	0	0	5	0	0
4. E.B.	F	50	11/5/58	None	——	——	109	0	0	95	19	93
			12/20/58	D	1.0	45	56	0	0	64	21	53
			3/18/59	D	1.0	133	66	0	0	73	20	40
5. T.W.	M	53	1/22/58	None	——	——	98	0	0	83	4	12
			2/17/58	TOH	16	14	165	4	24	163	17	99
			9/24/58	TOH	6	219	62	0	0	72	20	134
			1/2/59	D	2.5	73	—	0	0	—	—	—
			5/12/59	D	2.5	203	49	0	0	68	5	20
6. J.S.	M	60	2/17/58	None	——	——	92	30	19	143	41	312
			4/16/58	TOH	8	56	83	25	186	164	76	1040
			11/13/58	TOH	8	263	126	30	137	130	35	178
			4/3/59	D	1.5	141	131	52	188	117	80	309
7. M.Mc.	F	51	1/15/58	None	——	——	75	—	—	99	25	209
			3/4/58	TOH	16	28	30	5	23	222	14	301
			10/28/58	TOH	10	234	63	11	20	130	55	245
			1/26/59	D	2	84	82	3	5	95	45	146
			3/31/59	D	2.5	64	64	0	0	71	36	94

8. O.S.	M	46	1/22/58	None	——	—	72	35	174	175	57	437
			2/20/58	TOH	16	25	84	26	150	272	65	625
			9/16/58	TOH	8	206	133	34	181	262	65	616
			3/24/59	D	1.5	155	59	0	0	136	52	337
9. E.L.	F	53	10/14/59	None	——	—	48	0	0	17	0	0
			1/5/59	D	1.75	77	37	0	0	20	0	0
			3/24/59	D	1.5	80	87	0	0	55	4	9
10. O.H.	F	66	12/19/58	TOH	6	160	29	0	0	26	0	0
			1/30/59	D	1.5	41	26	0	0	45	0	0
11. E.K.	F	56	2/1/58	None	——	—	25	0	0	45	51	86
			2/17/58	TOH	8	16	35	20	18	73	46	124
			10/19/58	TOH	6	242	19	0	0	107	79	500
			1/22/59	D	1.5	95	60	0	0	92	67	220
12. T.F.	F	63	4/25/57	None	——	—	13	12	5	43	29	49
			6/10/57	Tdac	8	14	47	0	0	40	0	0
			2/11/58	TOH	6	241	53	5	—	99	40	145
			1/15/59	D	1.6	115	50	0	0	60	15	35
13. W.Mc.	M	66	5/11/57	TOH	5	43	127	49	229	145	74	309
			12/30/58	TOH	6	142	39	18	19	146	38	194
			3/24/59	D	1.0	64	55	19	37	201	83	649
14. H.N.	M	46	1/30/59	D	0.75	138	63	10	29	286	66	707
			3/25/59	D	1.0	54	193	4	41	236	42	342

*Pred = Prednisone acetate
Tdac = Triamcinolone diacetate
TOH = Triamcinolone (alcohol)
D = Dexamethasone

†These values are the combined figures for the 4 specimens before and after histalog stimuvation respectively

‡Output equals Volume × Clinical Units × 0.00365 × 10

§Cl.U. = Clinical Units

blood sugar determinations in 26 different patients taken at varying intervals during dexamethasone therapy were normal.

There were many additional adverse side reactions (Table 1). Moon facies and ecchymoses were very frequent, occurring in 26 and 14 patients respectively. Moon facies in 6 instances and ecchymoses in 5 were more prominent with dexamethasone than with previously administered triamcinolone. The reverse did not happen. Hirsutism occurred in 7 individuals and to the same degree as with triamcinolone.

There was no diminution in weight at the end of the first week of treatment, suggesting that no significant diuresis occurred. On the contrary, 19 of 42 patients weighed during this interval had an increase in weight of 2 or more pounds. A weight gain of 3 or more pounds at the termination of the study period occurred in 40 individuals. Of these, 19 gained 10 or more pounds, the maximum being 27. These alterations in weight were observed regardless of therapy during the control period. Increased appetite occurred in 25 patients. Gastrointestinal symptoms, such as nausea, eructations, and pyrosis, were observed in 15. Bloating occurred in 8 individuals and caused marked discomfort in 6. This bloating was markedly exaggerated in comparison with that noted with triamcinolone therapy.

Another effect of dexamethasone was edema which developed in 9 individuals. The edema was constant in 5 patients; there was no attempt at salt restriction. No significant electrolyte alterations in sodium, potassium, and chloride were found in 26 patients in whom a total of 47 determinations were made at varying intervals during the study. Acute studies were not done with initial dosages.

Another toxic manifestation of interest was glossitis in 2 cases. The incidence of osteoporosis was not evaluated since the duration of the study was not sufficient for an accurate quantitation of this complication. However, there were no complaints of bone pain which would have been suggestive of osteoporosis. Hypertension did not occur, nor was there any evidence of psychosis.

The effect of dexamethasone on gastric juice production is illustrated in Table 2. Occasional patients, such as W.Mc., had an increase in output in the post-histalog specimens; however, there were others, like patient O.S., who had a decrease in output. Most individuals showed only minor changes. The figures reveal no consistent trend towards an increase in hydrochloric acid formation with the basal or the post-histalog periods.

Roentgenograms of the upper gastrointestinal tract revealed peptic ulceration in 4 patients (Table 3). The first (T.W.), had no gastrointestinal symptoms or roentgenographic abnormalities with previously administered triamcinolone, but developed a duodenal ulcer after 4 months of dexamethasone. Gastric juice production was low in this patient (Table 2). The second (W.Mc.) had a pyloric ulcer which was first noted during triamcinolone therapy; this ulcer healed prior to this study while still on triamcinolone, but with the addition of an antiulcer regimen. The output of hydrochloric acid in the post-histalog gastric juice specimens in this individual was increased; basal secretion was not significantly altered (Table 2). The third patient (A.Sc.) developed an asymptomatic duodenal ulcer after 78 days of dexamethasone therapy; the average daily maintenance dose was 1.25 mg. A pyloric channel ulcer in the fourth patient (A.S.) may have been present before steroid administration.

TABLE 3.—CORRELATION OF DURATION OF TREATMENT AND DOSE OF DEXAMETHASONE WITH RESULTS OF UPPER GASTROINTESTINAL ROENTGENOGRAMS IN 25 PATIENTS WITH RHEUMATOID ARTHRITIS

Patient	*Duration of Therapy at Time of Last Barium Meal (days)*	*Average Daily Maintenance Dose (mg.)*	*Results of Roentgen-ray*
1. F.M.	245	1.5	Negative
2. J.S.	133	1.5	Negative
3. E.K.	170	1.5	Negative
4. E.L.	180	1.5	Negative
5. O.S.	169	1.5	Negative
6. M.Mc.	77	2.0	Negative
	168	2.25	Negative
7. O.H.	135	1.5	Negative
8. T.W.	157	2.5	Duodenal ulcer; none with previous triamcinolone therapy
9. E.B.	160	1.25	Negative
10. R.B.	260	1.5	Negative
11. T.F.	178	2.0	Duodenal ulcer with triamcinolone which healed and didn't recur with dexamethasone
12. C.H.	57	1.75	Negative
	225	1.75	Negative
13. M.M.	238	1.0	Negative
14. T.S.	227	1.75	Negative
15. S.M.	253	1.0	Negative
16. A.W.	180	1.5	Scarred duodenal bulb on control with no change during dexamethasone
17. H.N.	78	1.0	Negative
	199	1.5	Hypertrophic gastritis
18. W.Mc.	66	1.0	Pyloric ulcer with triamcinolone which healed, but recurred with dexamethasone
19. J.G.	145	0.75	Negative
20. E.A.	172	1.5	Negative
21. A.Sc.	78	1.25	Duodenal ulcer; no control Roentgen-rays
22. E.L.	190	1.25	Negative
23. M.S.	35	1.5	Negative
24. A.S.	300	0.75	Pyloric ulcer
25. R.F.	144	1.5	Negative

The ulcer had been noted first 4 years previously, but a repeat barium meal was not performed until the patient had already received dexamethasone. Another individual with a previously diagnosed "irritable duodenal bulb" showed no change during dexamethasone therapy. Most of the 25 patients with barium meals had been receiving 1.5 to 2.0 mg. of dexamethasone daily for 6 months.

Dexamethasone was discontinued after varying periods of treatment in 23 patients for the reasons noted in Table 4. Bloating, edema, and unsatisfactory anti-inflammatory response

were each responsible in 3 instances. One patient expired of unrelated coronary artery disease.

Discussion. Dexamethasone is an effective anti-rheumatic agent whose potency is greater than other steroids utilized for the treatment of rheumatoid arthritis. However, this augmented anti-rheumatic potency as determined by weight comparisons of different steroids does not imply superiority. Of clinical import is whether this anti-inflammatory response is still greater when maintenance doses of the various steroids are tested, and whether this smaller dose by weight is accompanied by fewer or milder side effects. Our results do not indicate that such is true for dexamethasone. The diminution of synovitis generally was no greater when compared to triamcinolone. Complicating side effects of dexamethasone were at least as common and severe as those of other anti-inflammatory steroids. Moon facies, hirsutism, and ecchymoses were prevalent, and, in several instances, more so than with triamcinolone. Gastrointestinal complaints of bloating, gas, and epigastric burning were not unusual, while the bloating was particularly distressing. Increased appetite and weight gain were disturbing in many patients. Although none of the causes listed in Table 4 for discontinuing dexamethasone include weight gain, this factor will probably necessitate the cessation of such therapy in several patients in the near future. Edema was a surprising complication in 17% of our cases although no abnormalities were noted in blood electrolytes. Also, the possible decreased diabetogenic effect expected because of animal studies was not substantiated by our series, but a longer period of evaluation would be necessary to critically analyze this item.

TABLE 4.—REASONS FOR DISCONTINUATION OF DEXAMETHASONE THERAPY IN 54 PATIENTS WITH RHEUMATOID ARTHRITIS

Cause	*Number of Patients*
No further need for steroid	7
Bloating	3
Edema	3
Loss of contact with patient	3
Unsatisfactory anti-inflammatory effect	3
Ecchymoses	1
Glycosuria	1
Deceased (coronary artery disease)	1
Peptic ulcer	1

Similarly a longer period of observation would be necessary to evaluate the incidence of peptic ulceration as a complication of dexamethasone therapy. The data obtained indicate that gastric juice production was not significantly altered by dexamethasone; results were similar to those previously reported by the authors in reference to triamcinolone[5]. The mechanism of peptic ulcer formation in these patients would appear not to be dependent on increased gastric juice production.

It seems probable that dexamethasone offers no advantages over other anti-inflammatory steroids for the treatment of rheumatoid arthritis.

Summary. Dexamethasone is another new synthetic anti-rheumatic steroid which does not satisfy the criteria for a potent anti-inflammatory drug with a minimum of undesirable physiological side effects. Undesirable reactions to dexamethasone were at least as frequent as with other steroids, in some instances more prominent. Noteworthy were the edema, the marked bloating, increased appetite and weight gain. The diabetogenic effect requires further evaluation; however, preliminary information from our studies suggests that there may not be a decrease in

diabetes as a complication. Peptic ulceration developed in 4 patients; the true incidence of this side effect requires additional study. Dexamethasone caused no consistent alteration in gastric juice production.

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SUMMARIO IN INTERLINGUA

Therapia a Dexamethasona, con Studios de Function Gastric in Patientes con Arthritis Rheumatoide

Dexamethasona es un addition al lista del nove synthetic steroides antirheumatic que non satisface le criterios de un potente droga anti-inflammatori con un minimo de indesirabile effectos physiologic secundari. Le reactiones indesirabile evocate per dexamethasona esseva al minus tanto frequente como illos producite per altere steroides, e in certe casos illos esseva plus prominente. Notabile inter iste reactiones esseva edema, marcate inflation abdominal, accrescimento de appetito e augmento de peso. Le effecto diabetogenic require un evalutation additional; nonobstante, le informationes preliminari resultante de nostre studios indica que un reducite frequentia de diabete como complication probabilemente non essera trovate. Ulceration peptic se disveloppava in 4 patientes; le determination del ver frequentia de iste effecto secundari requirera studios additional. Dexamethasona causava nulle alterationes uniforme in le production del succo gastric.

SUBLINGUAL ERYTHROL TETRANITRATE IN THE TREATMENT OF ANGINA PECTORIS. EFFECT OF VARYING THE DOSE AND RATE OF ADMINISTRATION*

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In a previous publication[2], it was demonstrated that many nitrites are highly effective in the treatment of patients with angina pectoris when administered sublingually, buccally, by hypodermic injection, or by inunction, whereas, in contrast, these drugs are considerably less effective when swallowed. Of the six nitrites tested (nitroglycerin, erythrol tetranitrate, pentaerythritol tetranitrate, mannitol hexanitrate, triethenolamine trinitrate, and sodium nitrite), erythrol tetranitrate administered sublingually or buccally was of greatest value in the prophylactic therapy of angina pectoris.

At the time the above studies were performed, the only preparations of erythrol tetranitrate available consisted of 15-mg. and 30-mg. compressed tablets intended to be swallowed. These tablets†, when administered under the tongue or in the buccal pouch, required from one-half to one and one-half hours for complete disintegration and disappearance. Because of this prolonged dissolution time, buccal administration proved more comfortable than the sublingual route. It was suspected that the prolonged duration of action of these sublingual tablets might be attributed, at least in part, to the prolonged time required for dissolution and hence a prolonged period of absorption into the blood stream. More recently, tablets of erythrol tetranitrate with different rates of dissolution and varying dosages have been prepared.‡ The present study was undertaken to determine if a prolonged dissolution time was essential for a prolonged therapeutic effect and to determine the effect of varying doses of erythrol tetranitrate.

*This study was aided by a grant from Burroughs Wellcome & Company (U.S.A.), Inc.

†Marketed by Burroughs Wellcome & Company (U.S.A.), Inc., Merck & Company, and Sharp & Dohme Division of Merck & Company.

‡Supplied by the Burroughs Wellcome & Company (U.S.A.), Inc. Available as Cardilate, 5 mg. and 10 mg. tablets.

Material and Methods. As in previous studies (Riseman, Altman and Koretsky[2], Riseman and Brown[3,4]), patients were interviewed weekly, and the value of each preparation was determined not only by the frequency of anginal attacks in daily life, but especially by the amount of work each patient could perform under standardized conditions before developing angina. The Standardized Exercise Tolerance Test (Riseman, Altman and Koretsky[2], Riseman and Stern[6]) used in this study consisted of having the patient repeatedly mount and descend a two-step staircase in a room with a constant cold temperature of 45° F. to 55° F. until an attack of angina pectoris was induced. All tests were performed in the morning after a light breakfast. Only a single test was performed on a given day.

Fourteen patients with angina pectoris, presumably secondary to arteriosclerosis, served as subjects in this series. All patients had been studied for months to years before starting the present measurements, so that their usual exercise tolerance and frequency of attacks in daily life were well known.

As in previous studies (Riseman, Altman and Koretsky[2], Riseman, Steinberg and Altman[5]), the response to therapy was divided into three categories by comparing the Standardized Exercise Tolerance following medication with the maximum amount that could be performed while taking placebos.

MARKED RESPONSE. This indicates that, following therapy, the exercise tolerance in the laboratory was increased either by at least 50% before the patient was forced to stop because of angina or by at least 25% without pain, the exercise being stopped by the patient because of dyspnea or fatigue.

MODERATE RESPONSE. Following medication the exercise tolerance was increased by 20% to 49% before the patient developed angina, or else he was able to perform up to 24% more work without pain, but was forced to stop because of dyspnea or fatigue.

SLIGHT OR NO RESPONSE. Following treatment, the patient developed angina after less, the same or no more than 19% more exercise under the standardized conditions than the maximum that was possible while taking placebos.

Since experience has shown that, in general, the ability to respond to vasodilators can be predicted by the patient's response to nitroglycerin, the subjects were divided into three groups according to whether they showed a marked response (Group 1), a moderate response (Group 2), or a slight or no response (Group 3) 2 minutes after the sublingual dissolution of 0.3 mg. of nitroglycerin.

Several preparations of erythrol tetranitrate with varying rates of dissolution were prepared and studied, but for the purpose of this presentation only those with either a rapid or a prolonged dissolution time were compared. Since erythrol tetranitrate is only sparingly and slowly soluble, the term "dissolution time" (that is, the time required for complete disappearance of all material, after it has been placed under the tongue or in the buccal pouch) is preferable to disintegration time" or "solution time."

The preparations with rapid dissolution time were of two types:

1. Pure erythrol tetranitrate was combined with enough lactose so that the total volume of material (in powder form) was the same despite varying dosages of 1 mg., 5 mg., 10 mg., or 15 mg. of active medication. Individual doses were stored in hard gelatin capsules which were emptied into the buccal or sublingual pouch in order to test the response to a single dose.
2. Compressed elongated tablets were prepared especially for sublingual or buccal administration. These tablets contained either 5 mg., 10 mg., or 15 mg. of erythrol tetranitrate, but were all identical in appearance and dissolution time. These were used to evaluate the effect of taking medication repeatedly, three times daily, as in clinical practice. After one to several weeks of such therapy, the Standardized Exercise Tolerance Test was performed at intervals of a few minutes, 1, 2, 3, or 4 hours after dissolution of the morning dose.

The preparations with prolonged dissolution time consisted of sublingual tablets identical in appearance with those described above, but prepared with a dissolution time comparable to the oral tablets which had been used in the previous study (Riseman, Altman and Koretsky[2]).

Placebos, identical in appearance with the sublingual tablets described above, were used also. Neither the patient nor the observer of the Standardized Exercise Tolerance Test knew if the sublingual tablets used were placebos or erythrol tetranitrate.

COMPARISON OF BUCCAL AND SUBLINGUAL DISSOLUTION TIME. All mate-

rials studied disappeared more rapidly and more uniformly from the sublingual region than from the buccal pouch.

The dissolution time was found to vary considerably with the amount of saliva in the mouth, the presence of lower dentures (which limit the amount of absorbing mucous membrane in the buccal pouch), and especially with the amount of agitation with the tongue or sucking of the pill by the patient. To eliminate the latter, patients were cautioned not to disturb the powder or sublingual tablet after it had been positioned.

The erythrol tetranitrate powder disappeared from under the tongue in 1 to 10 minutes (with a rare exception). The same material usually required about 10 minutes longer to disappear from the buccal pouch of the same patients.

The compressed sublingual tablets of erythrol tetranitrate with rapid dissolution time disappeared from under the tongue in 2 to 10 minutes in all patients. In contrast, the same material required from 20 to 50 minutes to disappear from the buccal pouch of 13 out of 15 subjects (Fig. 1).

The sublingual tablets with prolonged dissolution time disappeared from under the tongue in 15 to 30 minutes in 12 out of 16 patients, whereas this material required 20 to 75 minutes to disappear from the buccal pouch in all patients (Fig. 1).

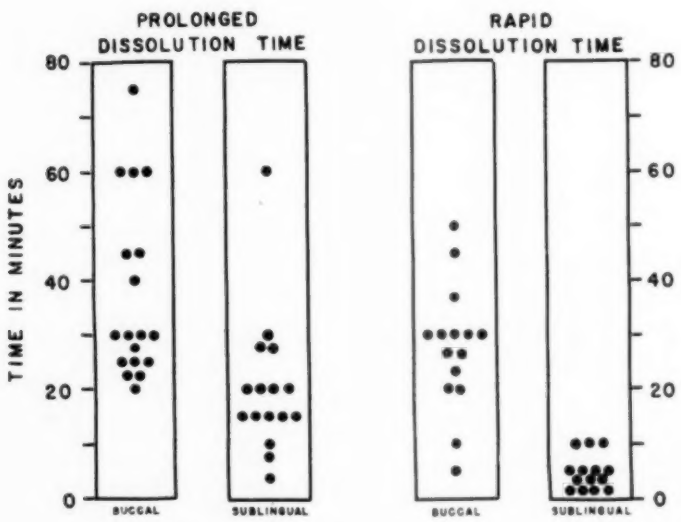

Fig. 1.—Comparative speed of buccal vs. sublingual disappearance of erythrol tetranitrate.

In general, the rate of absorption sublingually was more constant and required, on an average, about 20 minutes less than from the buccal pouch.

EFFECTIVENESS OF PREPARATIONS WITH SHORT DISSOLUTION TIME. As in the previous study (Riseman, Altman and Koretsky[2]), the Group 3 patients showed no significant increase in ability to perform the Standardized Exercise Tolerance Test following the sublingual or buccal administration of 15

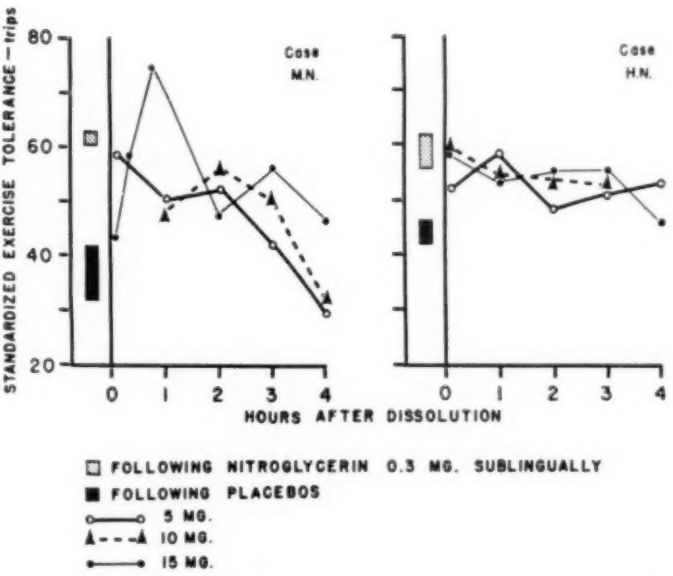

Fig. 2.—The response to single doses of erythrol tetranitrate powder administered sublingually as measured by the Standardized Exercise Tolerance Test.

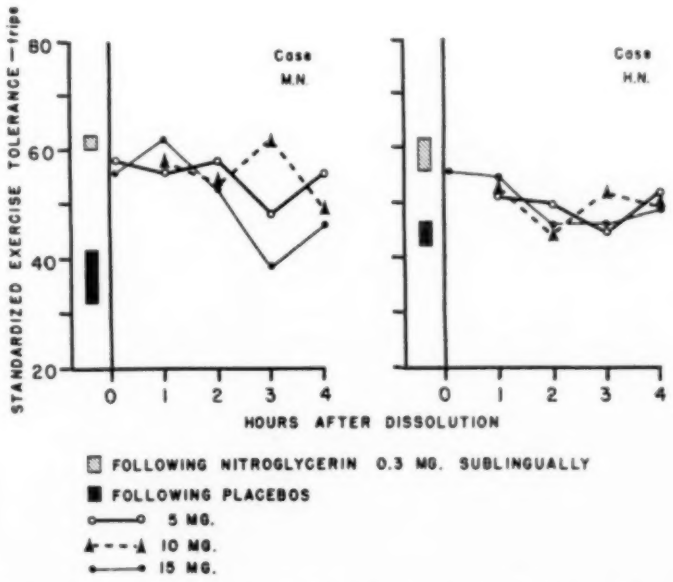

Fig. 3.—The response to repeated doses of erythrol tetranitrate tablets administered sublingually as measured by the Standardized Exercise Tolerance Test.

TABLE 1.—INCREASE IN STANDARDIZED EXERCISE TOLERANCE TEST FOLLOWING ERYTHROL TETRANITRATE POWDER AT VARYING TIME INTERVALS AFTER SUBLINGUAL DISSOLUTION

						Percent Increase in S.E.T.T. Following Therapy					
						Erythrol Tetranitrate Powder Sublingually					
							Time Interval Following Dissolution				
	Patient	*Sex*	*Age*	*Usual S.E.T.T. Trips—Placebos*	*Nitroglycerin S.L. 0.3 mg.*	*Dose-mg.*	*1mm.*	*1 hr.*	*2 hr.*	*3 hr.*	*4 hr.*
Group 1	M.Rs.	F	47	17-24	321+	*15*	317	183	75	100	50
						10	—	321	217	25	−8
						5	50	37	13	—	—
	F.P.	F	63	24-32	109	*15*	66	128	47	25	28
						10	75	35	47	53	25
						5	59	47	35	9	—
	M.Rl.	F	54	26-38	71	*15*	11	68	5	121	163+
						10	—	—	—	—	—
						5	—	163+	163+	153	—
	M.Rz.	M	55	29-34	65	*15*	−12	23	6	23	—
						10	—	53	6	−26	−6
						5	−12	—	—	—	—
Group 2	H.N.	M	72	42-46	35+	*15*	22	13	17	17	4
						10	26	26+	17	13+	−4
						5	13	26	4	13	9
	M.N.	F	71	32-42	43	*15*	2	76	12	33	9
						10	38	14	33	19	−24
						5	38	19	24	0	−24
	S.K.	F	64	15-22	27	*15*	9	−5	9	18	—
						10	—	14	0	—	—
						5	4	—	—	—	—
	J.L.	F	65	18-23	26	*15*	17	—	—	—	—
						10	70	61	70	−4	—
						5	35	44	57	61	
Group 3	R.B.	M	67	16-20	10	*15*	10	10	5	−5	10
						10	5	15+	35	10	5
						5	—	—	—	—	—

S.E.T.T., Standardized Exercise Tolerance Test

\+ No attack of angina pectoris induced.

— A decrease in exercise tolerance as compared with the *maximum* amount that could be performed during the placebo trial.

S.L., Medication administered sublingually.

TABLE 2.—INCREASE IN STANDARDIZED EXERCISE TOLERANCE TEST FOLLOWING ERYTHROL TETRANITRATE SUBLINGUAL TABLETS WITH RAPID DISSOLUTION TIME AT VARYING INTERVALS AFTER DISSOLUTION

						Percent Increase in S.E.T.T. Following Therapy				
						Erythrol Tetranitrate Sublingual Tablets (Rapid Dissolution)				
				Usual S.E.T.T. Trips—Placebos	*Nitroglycerin S.L. 0.3 mg.*		*Time Interval Following Dissolution*			
	Patient	*Sex*	*Age*			*Dose-mg.*	*Imm.*	*1 hr.*	*2 hr.*	*3 hr.*	*4 hr.*
Group 1	F.P.	F	63	24-32	109	*15*	63	38	28	38	44
						10	—	25	13	19	34
						5	—	31	19	19	31
	M.Rz.	M	55	29-34	65	*15*	−12	18	0	0	−5
						10	—	12	−17	53	−5
						5	—	12	−17	−23	—
	H.N.	M	72	42-46	35+	*15*	27	17	0	0	4
						10	—	13	−4	13	4
						5	—	13	9	0	13
Group 2	M.N.	F	71	32-42	43	*15*	33	48	23	−14	10
						10	—	38	23	48	17
						5	38	33	38	14	33
	J.L.	F	65	18-23	26	*15*	17	—	—	—	—
						10	69	65	0	9	—
						5	—	34	0	−9	—
Group 3	J.H.	M	67	15-22	14	*15*	—	—	—	—	—
						10	—	23	—	—	—
						5	—	−23	−14	−32	−9
	R.B.	M	67	16-20	10	*15*	20	10	0	10	—
						10	—	5	10	—	—
						5	—	20	20	10	—
	E.M.	M	64	60-70	9	*15*	6	6	−3	0	—
						10	—	—	—	—	—
						5	—	0	−3	0	0

S.E.T.T., Standardized Exercise Tolerance Test

\+ No attack of angina pectoris induced.

— A decrease in exercise tolerance as compared with the *maximum* amount that could be performed during the placebo trial.

S.L., Medication administered sublingually.

mg. of the erythrol tetranitrate in any of the forms used. The response to medication is shown best, therefore, by the results in Group 1 and Group 2 patients, especially those tested with all 3 doses employed and at many different time intervals after dissolution of the tablet.

Following the administration of single 15-mg. doses of erythrol tetranitrate powder, the capacity for increased exercise tolerance usually began within a few minutes, reached its peak at 1 to 2 hours, and then decreased with a beneficial effect for 3 to 4 hours (Table 1), (Fig. 2). Similar effect was observed following the administration of single 5-mg. or 10-mg. doses of erythrol tetranitrate powder. It is evident that in some patients, the 5-mg. sublingual tablets are as effective as those containing 10 mg. or 15 mg. (Table 2), Fig. 3). This is in accord with previous studies (Riseman and Brown[3]), wherein it was found that doses of nitroglycerin as small as 0.13 mg. were effective in Group 1 patients.

The effects of doses larger than 15 mg. were measured by administering 30 mg., 45 mg., or 60 mg. (2, 3, or 4 tablets respectively) sublingually, 3 times daily, for at least one week, to patients who failed to respond to 15 mg., unless these higher dosages could not be tolerated because of headache or light-headedness. None of the 5 patients so tested showed any significant increase in exercise tolerance 1 to 2 hours after these large doses (Table 3).

TABLE 3.—CHANGE IN STANDARDIZED EXERCISE TOLERANCE TEST FOLLOWING LARGE DOSES OF ERYTHROL TETRANITRATE ADMINISTERED SUBLINGUALLY TO PATIENTS WHO SHOWED LITTLE OF NO RESPONSE TO 15 mg. DOSES

				Percent Increase in S.E.T.T. Following Therapy				
					Erythrol Tetranitrate Sublingual Tablets			
Patient	*Sex*	*Age*	*Usual S.E.T.T. Trips - Placebos*	*Nitroglycerin S.L. 0.3 mg.*	*15 mg.*	*30 mg.*	*45 mg.*	*60 mg.*
S.K.	F	64	15-22	27	—5	—23	—	—
L.A.	F	57	11-19	14	—31	—53	—47	—
J.H.	M	67	15-22	14	0	0	5	8
R.B.	M	67	16-20	10	10	10	10	0
B.S.	F	69	26-33	0	—6	6	3	—

S.E.T.T., Standardized Exercise Tolerance Test

— A decrease in exercise tolerance as compared with the *maximum* amount that could be performed while taking placebos.

S.L., Medication administered sublingually.

SIDE EFFECTS. *Local Burning.* Several patients reported mild local burning at the point of contact of the erythrol tetranitrate with the oral mucous mem-

brane during the period of dissolution. This disappeared 5 to 10 minutes thereafter. When the sublingual tablets with rapid dissolution time were used, this was distinctly less severe and, of course, less prolonged. In no case was this a deterrent to continued use of the drug.

Headache. As in the previous study (Riseman, Altman and Koretsky[2]), few of the patients in this series complained of headache after 15 mg. of erythrol tetranitrate sublingually. This symptom has been observed frequently, however, in larger groups of patients treated in private practice. The headache usually disappears spontaneously or following aspirin. No cephalalgia occurred following 5-mg. sublingual tablets.

Dizziness, Light-headedness or Faintness. Several patients reported mild dizziness, light-headedness or faintness after the sublingual administration of the 15-mg. sublingual tablets with rapid dissolution time. This was especially noticeable on rising suddenly from a recumbent position. One patient fainted on walking to the kitchen about one-half hour after awakening and taking a 15-mg. sublingual tablet while still in bed. There were no residual effects and subsequent administration of the same dosage to the same patient produced no adverse responses. Similar reactions have been reported after sublingual nitroglycerin (Proger and Ayman[1], Sprague and White[7]). No dizziness, light-headedness, faintness or syncope were observed following the 15-mg. sublingual tablets with a prolonged dissolution time or following the 5-mg. or 10-mg. sublingual tablets with rapid dissolution time.

Hypotension. For many years, erythrol tetranitrate has been prescribed as oral tablets (to be swallowed) for the treatment of hypertension. Measurements of the blood pressure following the sublingual or buccal tablets with prolonged dissolution time revealed no significant change. However, after the sublingual administration of erythrol tetranitrate with rapid dissolution time, a moderate decrease in blood pressure, chiefly in the systolic component, was frequently observed. This is probably related to the occasional complaint of light-headedness after the sublingual administration of 15-mg. tablets with rapid dissolution time. Following the 5-mg. doses, there was complete absence of such symptoms.

Most of the patients in the present series were normotensive, or at most border-line hypertensive. Further study with hypertensive patients will be necessary in order to determine the value of erythrol tetranitrate with rapid dissolution time, administered sublingually, in the treatment of hypertension.

Summary. Erythrol tetranitrate is absorbed more rapidly and uniformly from the sublingual area than from the buccal pouch.

The prolonged duration of the beneficial effects of erythrol tetranitrate in patients with angina pectoris is evident following sublingual administration of erythrol tetranitrate with rapid dissolution time. Therefore, the prolonged beneficial effect of erythrol tetranitrate is not dependent upon prolonged absorption.

The 5-mg. sublingual tablets with rapid dissolution time are less frequently followed by undesirable side effects and in some patients are as effective as larger doses.

Doses as large as 30 mg., 45 mg., and 60 mg. were not effective in patients who failed to respond to 15 mg. doses.

The sublingual administration of erythrol tetranitrate with a rapid dissolution time was followed in some patients by a moderate decrease in systolic blood pressure.

TABLE 4.—BLOOD PRESSURE FOLLOWING SUBLINGUAL ADMINISTRATION OF ERYTHROL TETRANITRATE WITH RAPID DISSOLUTION TIME

		Blood Pressure Readings									
			Following Erythrol Tetranitrate								
			Powder					*Tablets*			
Patient	*Dose in mg.*	*Control No Medication*	*Immediately*	*1 hr.*	*2 hr.*	*3 hr.*	*4 hr.*	*Immediately*	*1 hr.*	*2 hr.*	*3 hr.*	*4 hr.*
M.Rs.	*15*	146/90		106/72	110/82	132/90	130/80					
	10											
	5		130/88	118/80	132/80							
F.P.	*15*	168/88	136/80	140/76	136/72	132/66	128/66 134/70		132/88 120/80	140/80 180/84	136/90	160/80
	10											
	5				128/68	142/72			106/72	140/76	150/88	
M.Rl.	*15*	118/82	104/78	80/58	100/76	96/70						
	10											
	5		108/72	98/84	120/76							
M.Rz.	*15*	124/86		108/80	90/70	88/70				110/90		142/94
	10			92/68	120/70	110/72	120/70		118/80	134/84	136/90	120/70
	5		118/96					118/96	116/76	120/90		

	15					103/78	110/74		114/74		130/80	138/80	
H.N.	*10*	120/80	120/80	112/76	118/76	116/70	110/70		120/80	120/80			
	5			114/70	120/74	112/72				116/66	148/84	98/60	
	15					104/62	96/66		128/82	100/80	150/80		
M.N.	*10*	148/80		118/80	114/80	124/90	118/60		106/72	118/80	130/90	168/102	
	5		140/88	110/70	120/76	120/80		140/88	118/80	144/86	150/90	128/90	
	15		162/86	150/70		152/70							
S.K.	*10*	170/80			134/90								
	5		150/76										
	15		112/60					112/60	110/72		120/70		
J.L.	*10*	126/68		120/74	104/64								
	5		130/68	118/58	114/70	102/58		130/68	120/70	120/70	114/70		
	15		120/66		120/66	128/54	160/70	124/66	148/70	150/70	160/74		
R.B.	*10*	180/68	164/72	134/58	140/70	156/80	134/80		118/62	170/68			
	5								160/60	170/70			
	15			140/80					140/80	170/80			
L.A.	*10*	124/80											
	5												
	15								114/74				
J.H.	*10*	124/80							116/80	130/80	156/90	140/76	
	5												
	15												
E.M.	*10*	176/104											
	5									160/90	158/90	180/100	

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SUMMARIO IN INTERLINGUA

Tetranitrato Erythrolic Sublingual in le Tractamento de Angina de Pectore. Effecto de Variationes del Doses e del Rhythmo de Administration

Tetranitrato erythrolic es absorbite plus rapide- e uniformemente ab le area sublingual que ab le bursa buccal.

Le perduration del effecto benefic de tetranitrato erythrolic in patientes con angina de pectore es evidente post administrationes sublingual del droga con dissolution rapide. Il seque que le prolongate effectos benefic de tetranitrato erythrolic non depende del prolongation del absorption.

Tablettas sublingual de 5 mg con solution rapide es minus frequentemente sequite de adverse effectos lateral. In certe patientes illos es tanto efficace como doses plus grande.

Doses de 30, 45, e mesmo 60 mg non esseva efficace in patientes qui non respondeva a doses de 15 mg.

Le administration de tetranitrato erythrolic con dissolution rapide esseva sequite in certe patientes per un reduction moderate del tension de sanguine systolic.

THE EFFECT OF DISODIUM EDTA ON DIGITALIS INTOXICATION

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Calcium is known to play a regulatory role in myocardial function, a role which varies with its plasma concentration and which seems to be related to its influence on the myocardial cell membrane (Armitage, Burn and Gunning[1]). For many years, a synergistic mechanism has been postulated between calcium action and digitalis action (Gold and Edwards[5], Salter and Runels[8]), especially because of the similarity of the inotropic response of cardiac muscle to both factors. However, this is a controversial concept (Smith, Winkler and Hoff[12]), and it is more likely that digitalis depends on the presence of Ca^{++} ions at or inside the cell barrier to enhance its effect (Baker[2]) and, then, itself alters membrane permeability to cations (Hellems, Regan and Talmers[7]).

Both calcium and digitalis influence intracellular potassium levels, probably through changes in membrane permeability (Szent-Gyorgyi[14]). (These actions have been reviewed elsewhere [Seven[10]].) Lowering of plasma Ca^{++} levels appears to increase intracellular K^+ concentrations, the opposite effect from administration of Ca^{++} or digitalis preparations (Blackmon *et al.*[3], Hellems, Regan and Talmers[7], Schreiber[9]). After depolarization and the resultant passage of K^+ out of the cell, the calcium or digitalis action may increase the barrier to the reentry of K^+. It has been suggested that the contractile property of actomyosin (Szent-Gyorgyi[14]), or irritability of the cell, is most favored by an intracellular atmosphere of decreased K^+ concentration. However, the interactions here are complex, and some studies are contradictory.

Considering the three factors, calcium, digitalis, and potassium, our attempts at the therapy of myocardial hyperirritability, or arrhythmia, due to digitalis action have been in the realm of direct administration of potassium or the induction of hypocalcemia. Although potassium infusion often is effective in reducing myocardial irritability, its use may be dangerous and requires constant close observation. Of the methods available to counteract calcium action, intravenous disodium EDTA is most effective in producing a rapid, although transient, hypocalcemia. This compound reduces the level of ionized calcium by formation of a soluble calcium chelate, which then is excreted rapidly via the kidneys.

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Three grams of Na_2EDTA can be administered intravenously over a 20-minute period with little evidence of toxicity, other than "burning" in the vein of administration and occasional transient perioral and digital paresthesias. The former symptom is related almost entirely to the concentration of the chelating agent in the fluid medium (Seven[11]). A positive Trousseau sign is seen occasionally, but tetany is very rare. An occasional transient hypotension has been observed (Surawicz *et al.*[13]). The evidence of toxicity from larger doses or repeated administration, or both, has been reviewed elsewhere (Seven[11]).

Most investigators have used Na_2EDTA in doses of 0.6 to 4.0 gm. in the study of arrhythmias. Surawicz *et al.*[13] have reported an abolition of premature contractions in patients not receiving digitalis, as well as in those receiving this preparation. This suggests that Na_2EDTA cannot be administered to diagnose a state of digitalis overdosage. However, there are suggestions of some success in the therapy of suspected digitalis intoxication. Cohen *et al.*[4] infused 0.5 gm. Na_2EDTA or less to 6 patients with ventricular tachycardia who were receiving digitalis, and 5 showed a conversion to a normal sinus rhythm within 10 minutes after starting the drug. Gubner and Kallman[6] presented a patient showing digitalis intoxication and a supraventricular tachycardia with block, also converted to a normal sinus rhythm about 10 minutes after starting Na_2EDTA administration.

Because of the promise of therapeutic response in digitalis intoxication, we have studied a number of cases showing the clinical findings and arrhythmias associated with this state. We are presenting 6 short experimental reports illustrating the electrocardiographic response to intravenous administration of Na_2EDTA. Each patient was removed from digitalis medication prior to institution of chelation therapy, and each, with one exception, received 3 gm. of Na_2EDTA as a 1.2% solution in 5% glucose in water over a 20 to 30-minute period.

Case Reports. EXPERIMENT 1. A 72-year-old Negro woman with hypertensive heart disease had received 0.2 gm. digitalis leaf daily for 3 years. She developed nausea and vomiting 3 weeks prior to admission to the hospital. Digitalis therapy was stopped, and 10 minutes after start of 3.0 gm. Na_2EDTA her electrocardiographic findings of a Wenckebach phenomenon changed to a sinus rhythm with a prolonged P–R interval and occasional premature nodal beats (Fig. 1). A few days later, complete heart block was noted, which, during the next 9 days, spontaneously changed to a sinus rhythm with a P–R interval of 0.24 seconds and premature nodal contractions. On this day, Na_2EDTA shortened the P–R interval to 0.20 seconds but produced no effect on the premature nodal contractions (Fig. 2).

EXPERIMENT 2. A 44-year-old white man with moderate congestive heart failure and terminal hypertensive uremia was semicomatose when discovered, with no history available of previous digitalis therapy. Cardiac auscultation suggested mitral stenosis, and he was found to have a normal sinus rhythm on the electrocardiogram. Because of muscular twitching, he was given calcium gluconate in his parenteral fluids, and he also received 0.25 mg. Digoxin, intramuscularly, twice daily for 3 days. He then was discovered in severe shock with the arrhythmia shown in Fig. 3, and runs of contractions suggesting ventricular tachycardia. Na_2EDTA was administered, and the rapidly progressive changes to a sinus rhythm within 10 minutes are shown in Figs. 4 and 5. These electrocardiographic changes accompanied marked improvement in his clinical status.

A normal sinus rhythm was maintained for 2 days, when the patient again was given parenteral calcium and 2 doses of 0.25 mg. Digoxin over a 12-hour period. On the following day, his condition became suddenly critical, the electrocardiogram showing long runs suggesting ventricular tachycardia alternating with a nodal rhythm. When again given 3.0 gm. Na_2EDTA, he showed establishment of a continuous nodal rhythm within one minute and progressive changes to a normal sinus rhythm within 6 minutes. These electrocardio-

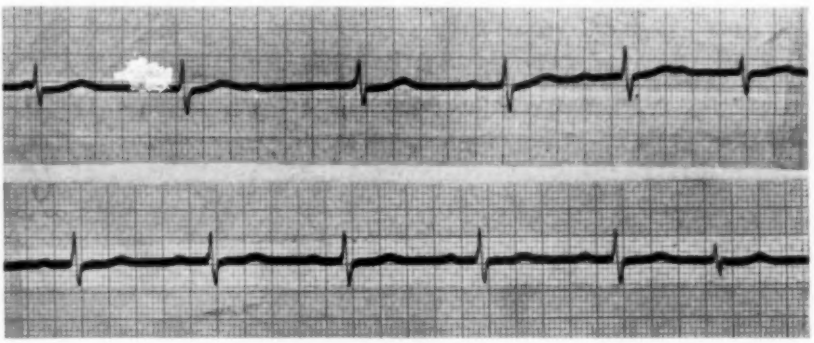

Fig. 1.—Experiment 1. Top tracing: before Na_2EDTA. Lower tracing: 10 minutes after start of infusion.

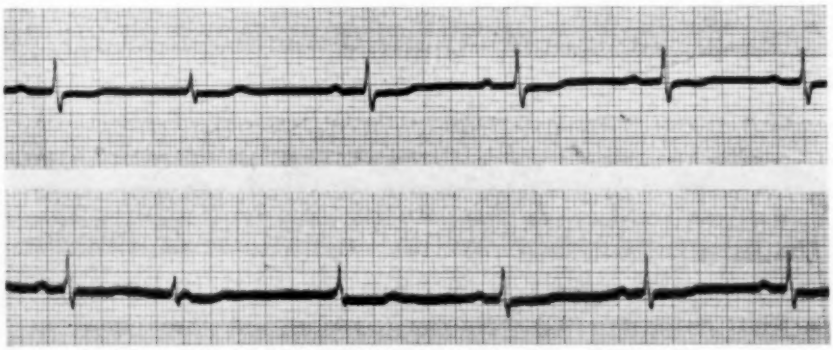

Fig. 2.—Experiment 1. Top tracing: before Na_2EDTA. Lower tracing: 10 minutes after start of infusion.

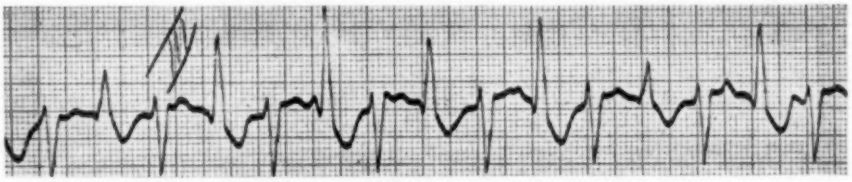

Fig. 3.—Experiment 2. Before Na_2EDTA.

graphic changes are shown in Fig. 6. Normal sinus rhythm persisted until his death 24 hours later.

EXPERIMENT 3. A 72-year-old white man complained of nausea, vomiting and epigastric distress over a 2-week period. He had received diuretic therapy and 0.1 mg. Digitoxin daily for 9 months in the treatment of congestive heart failure. After admission to the hospital, he was given 1.8 gm. Na_2EDTA, but no effect was produced on a presenting nodal tachycardia (Fig. 7). Under treatment with oral KCl for 24 hours, his arrythmia changed to a sinus tachycardia at a rate of 110 per minute. A gallop rhythm also was noted. When given 0.25 and 0.50 mg. Digoxin on 2 occasions and 0.8 mg. Cedilanid on one occasion, a nodal tachycardia of ap-

proximately 150 per minute was precipitated on each occasion, reverting in one or 2 days on oral KCl therapy.

EXPERIMENT 4. A 59-year-old Negro man with suspected arteriosclerotic heart disease and congestive heart failure for 6 months entered the hospital complaining of increasing shortness of breath at rest. He had received chlorothiazide and an unknown dosage of digitalis leaf for 3 months. His electrocardiogram revealed a sinus rhythm with regular premature ventricular contractions, which Na_2EDTA transiently converted to a normal sinus rhythm for 30 minutes (Fig. 8). Later, he was discharged from the hospital with a sinus rhythm and occasional premature ventricular contractions.

EXPERIMENT 5. A 36-year-old white man with multivalvular rheumatic heart disease presented himself with a history of nausea, vomiting, diarrhea and increasing shortness of breath over a 5-day period. He had been receiving 0.1 mg. Digitoxin daily for several years and chlorothiazide for the previous few months. The electrocardiogram revealed an atrial fibrillation-flutter pattern with long runs of coupling from premature ventricular contractions. Four minutes after Na_2EDTA was started, the premature contractions were abolished, leaving a regular nodal response (Fig.

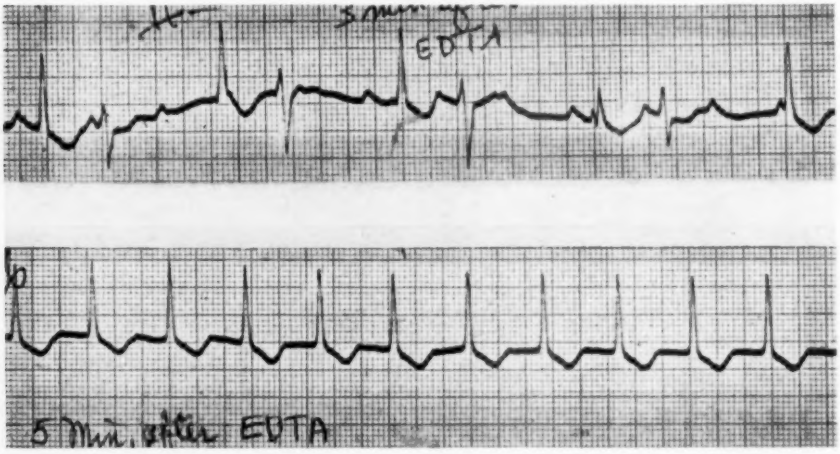

Fig. 4.—Experiment 2. Changes observed 3 to 5 minutes after start of infusion.

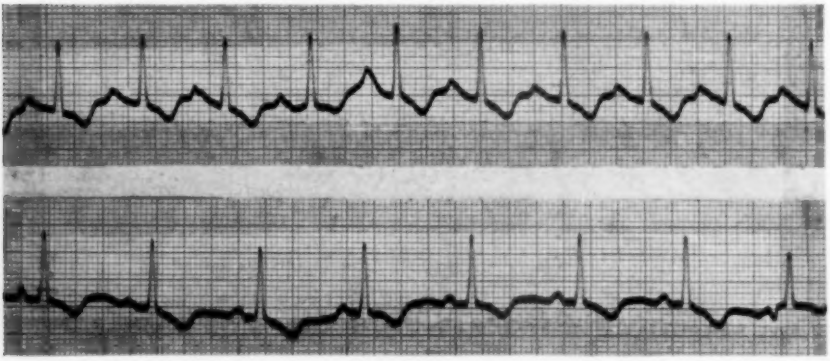

Fig. 5.—Experiment 2. Top tracing: 10 minutes after start of infusion. Lower tracing: 15 minutes after start of infusion.

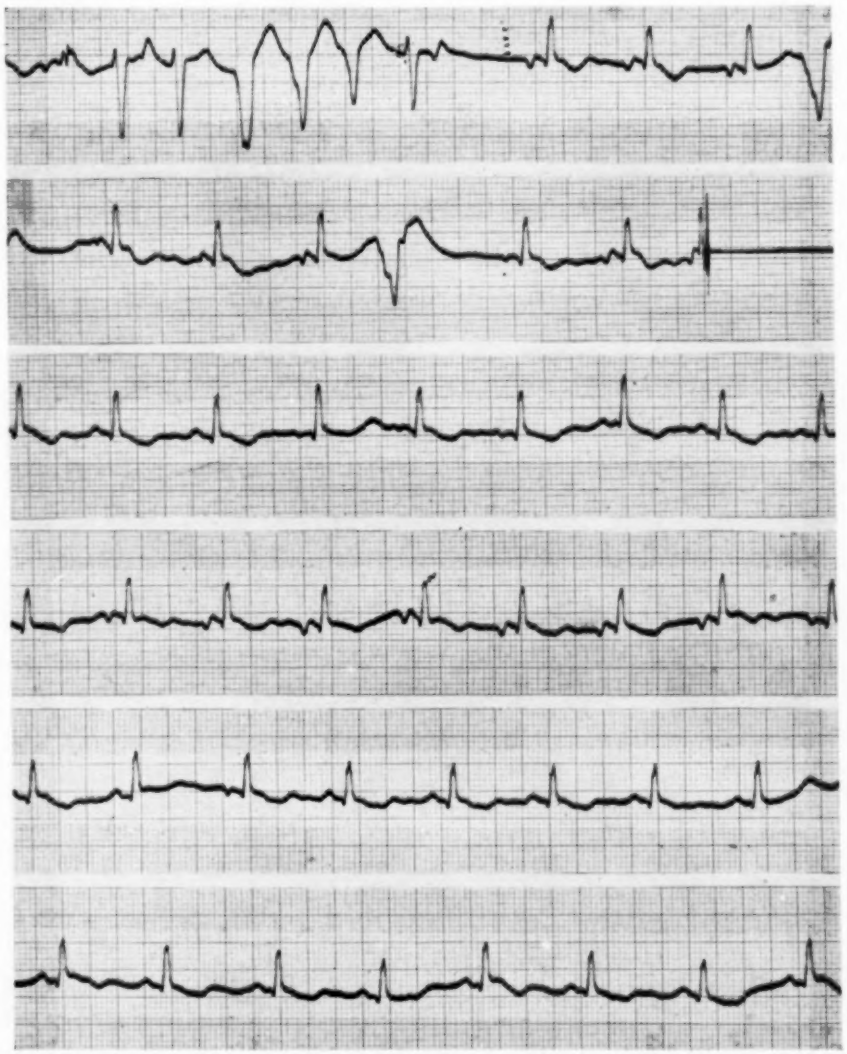

Fig. 6.—Experiment 2. The top tracing was taken before Na_2EDTA, the others, in order, ½ minute, 1 minute, 4 minutes, 6 minutes, and 10 minutes after start of the infusion.

9). Two hours later, a tripled rhythm occurred. After a few days on oral KCl therapy, he converted to a normal sinus rhythm, with complete remission of the presenting symptoms.

EXPERIMENT 6. A 76-year-old white woman with arteriosclerotic heart disease had had a pulmonary infarction 5 months prior to admission to the hospital and had been treated with 250 mg. chlorothiazide and 0.1 mg. Digitoxin on 2 out of every 3 days. Three weeks before admission, she developed intermittent fever and increasing shortness of breath. When first seen in the hospital, she was found to have electrocardiographic evidence of a sinus tachycardia with right bundle branch block and frequent premature ventricular contractions. Intravenous KCl had

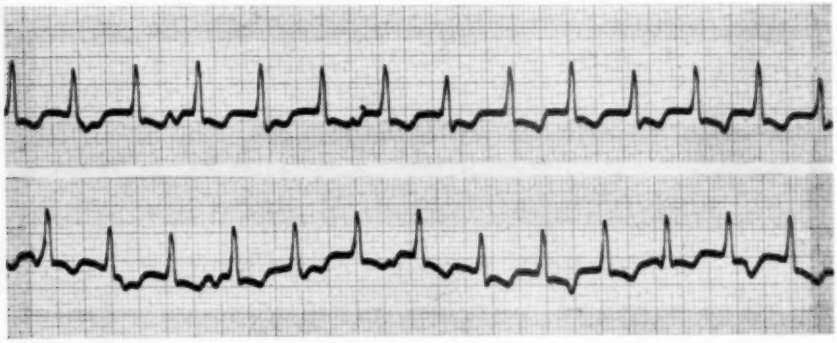

Fig. 7.—Experiment 3. Top tracing: before Na_2EDTA. Lower tracing: 10 minutes after start of infusion.

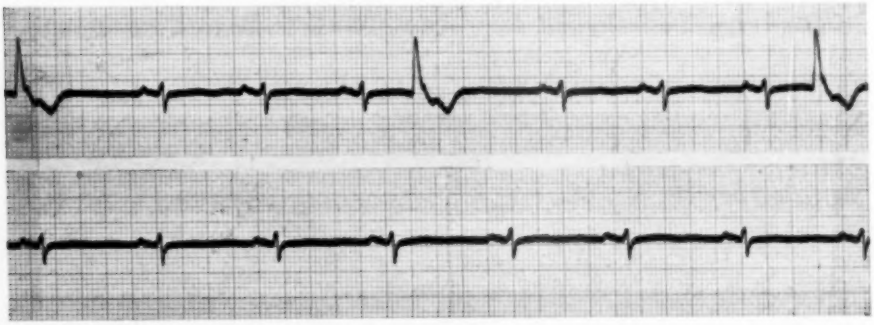

Fig. 8.—Experiment 4. Top tracing: before Na_2EDTA. Lower tracing: 10 minutes after start of infusion.

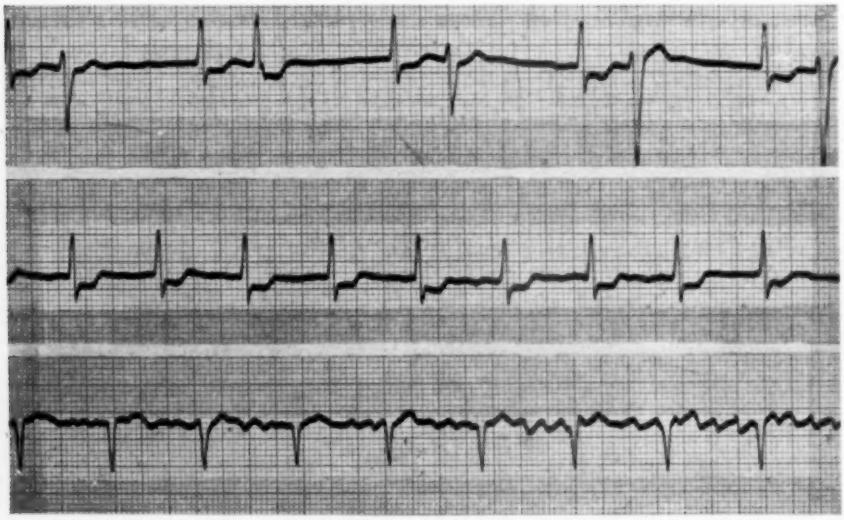

Fig. 9.—Experiment 5. Top tracing: before Na_2EDTA. Second and third tracings: 4 minutes and 10 minutes after start of infusion.

no effect on the premature contractions. She was given 1.0 mg. Digoxin orally on the second hospital day and 0.5 mg. on the third day, following which she suddenly developed a supraventricular tachycardia at a rate of 160 per minute. She then was given 0.6 mg. Cedilanid intravenously and, 45 minutes later, developed a ventricular rate of about 200 per minute with hypotension. Three grams of Na_2EDTA were administered, resulting within a few minutes in a slowing of the ventricular rate to about 100 per minute and some clinical improvement. However, about 10 minutes after the chelating agent was discontinued the ventricular rate slowly accelerated to its pretreatment rate. On the basis of this response to Na_2EDTA, further digitalis was not considered, and intravenous KCl was administered. However, the patient died 36 hours later with the supraventricular tachycardia unresolved.

Discussion. The simple clinical experiments presented here suggest that Na_2EDTA may produce a rapid response with reversion of electrocardiographic abnormalities in the presence of digitalis intoxication. That not every case will respond, however, is illustrated by the failure to change a nodal rhythm in Experiment 3 (Fig. 7). The beneficial effects observed in the other 5 experiments, especially the dramatic changes in Experiment 2, indicate that Na_2EDTA may be the treatment of choice for the induction of a rapid reversion of a dangerous arrhythmia in the presence of digitalis. Intravenous potassium therapy alone in digitalis intoxication often is effective in changing arrhythmias, but the administration must be carried out slowly with close observation. Although the effect of the chelating agent, Na_2EDTA, may be transient in some cases, its response persists in others, and it permits the institution of slower and more conventional KCl therapy after its administration has been completed within 20 to 30 minutes. As such, Na_2EDTA offers a rapid means of initial therapy in emergency situations. It should be emphasized again that arrhythmias not associated with digitalis may change under Na_2EDTA therapy, indicating that this method is not diagnostic of the presence of a digitalis intoxication state.

Three grams of Na_2EDTA can be given intravenously over a 20-minute period of time with safety and with only few side effects. No unusual toxic manifestations were observed in our patients.

The relationship of changes in arrythmias to serum calcium and potassium levels is not presented in this clinical report, since our review of methods and results of determinations has pronounced them unreliable in our cases. In each instance, however, values within normal ranges were obtained prior to Na_2EDTA therapy. It is likely that the clinical usefulness of this form of therapy will not depend on the necessity for determining serial potassium and calcium levels during and after administration of the chelating agent.

Summary. Experience with the use of Na_2EDTA in 6 cases of digitalis intoxication is reported. It is suggested that this chelating agent may be safely used as the first treatment for the dangerous arrhythmias, particularly those suggesting ventricular tachycardia, associated with toxic doses of this drug. Following its administration over 20 to 30 minutes, other forms of therapy may be instituted, if needed.

ACKNOWLEDGMENT: The Na_2EDTA used in this study was supplied in parenteral form through the cooperation of Dr. George Berryman of Abbott Laboratories.

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SUMMARIO IN INTERLINGUA

Le Effecto de Disodio-EDTA in Intoxication a Digitalis

Es reportate le experientia in le uso de Na_2EDTA in 6 casos de intoxication a digitalis. Es opinate que iste agente de chelation pote esser usate salvemente como le prime tractamento del periculose arrhythmias—particularmente illos que suggere tachycardia ventricular—associate con doses toxic de iste droga. Post su administration durante 20 a 30 minutas, altere formas de therapia pote esser instituite, si necessari.

THE EFFECT OF NYLIDRIN HYDROCHLORIDE (ARLIDIN) ON THE CEREBRAL CIRCULATION

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Cerebral vascular tone and blood flow are largely governed by the gaseous composition and acid-base equilibrium of arterial blood. Significant cerebral vasodilatation can be achieved consistently only by increasing arterial pCO_2, which is accomplished clinically by breathing gas mixtures containing CO_2. This, however, is extremely impractical for long-term therapy and has been employed chiefly in the management of acute cerebral infarctions. Agents such as nicotinic acid have enjoyed wide clinical use in persons with cerebral vascular disease in an attempt to increase cerebral perfusion; however, there is now ample evidence that nicotinic acid and similar agents do not actually augment cerebral blood flow (Scheinberg[5]).

The present investigation was undertaken to evaluate the cerebral vasodilatory properties of nylidrin hydrochloride (1[p-hydroxyphenyl]-2-[1′ methyl-3′ phenylpropylamino]-propanol, hydrochloride) (Arlidin)*. This is a synthetic epinephrine-like compound which has been used extensively in the treatment of peripheral vascular disease. That this drug might dilate cerebral blood vessels was suggested by Jacobson and Basar[3], who found that there was a 32% increase in retinal blood flow following oral nylidrin administration. The present study was not designed to evaluate the clinical effectiveness of this agent in persons with cerebral vascular disease. Moreover, it is not clear that augmenting cerebral blood flow is a particularly desirable therapeutic goal.

Materials and Methods. The majority of patients comprising this report had overt cerebral vascular disease; however, several normal persons were included. The entire spectrum of obliterative cerebral vasculopathy was studied, varying from persons with recurrent ischemic attacks to those with multiple infarctions and pseudo-bulbar palsy. Patients with fever, congestive heart failure, or recent myocardial infarction were excluded from the study; patients with mild to moderate anemia were included if there was no significant change in hemoglobin concentration during the treatment period. In most instances measurements were made when the

*The nylidrin hydrochloride used in this study was kindly supplied by U.S. Vitamin and Pharmaceutical Corporation.

TABLE 1.—CEREBRAL CIRCULATORY AND METABOLIC FUNCTIONS BEFORE AND AFTER THE ORAL ADMINISTRATION OF NYLIDRIN HYDROCHLORIDE (ARLIDIN)

	Subject	Age	Diagnosis	Dosage and Duration of Drug Administration	Cerebral Blood Flow (CBF) ml./min./100 gm.		Cerebral Vascular Resistance (CVR) mm.Hg/ml./min./100 gm.		Cerebral Oxygen Consumption ($CMRO_2$) ml./min./100 gm.		Mean Arterial Blood Pressure mm.Hg	
					C	Tr.	C	Tr.	C	Tr.	C	Tr.
Group Receiving Drug for periods less than 2 weeks	G.R.	68	"normal"	18 mg. t.i.d./11 d.	65	74	1.57	1.26	4.06	4.08	102	93
	G.B.	64	Cer. inf.	18 mg. t.i.d./12 d.	35	42	3.37	2.57	3.21	3.61	118	108
	O.C.	65	Cer. inf.	18 mg. t.i.d./8 d.	44	62	2.57	2.41	3.61	3.47	106	86
	C.C.H.	62	Cer. inf.	12 mg. t.i.d./8 d.	44	48	2.11	1.81	2.56	3.36	94	87
	A.D.	74	Cer. inf.	12 mg. t.i.d./7 d.	49	53	2.45	2.11	3.99	3.97	120	112
	L.S.	51	Cer. inf.	12 mg. t.i.d./11 d.	45	61	1.84	1.38	2.75	3.64	83	84
	G.J.	69	Cer. inf.	18 mg. t.i.d./8 d.	41 51*	30	2.54 1.94*	3.17	3.41 4.35*	1.99	104 99*	95
	H.E.	65	Diff. vas. dis.	18 mg. t.i.d./9 d.	35 49*	52	2.09 1.86*	1.58	1.93 3.41*	2.87	73 91*	82
	J.Mc.	71	Diff. vas. dis.	12 mg. t.i.d./5 d.	42	53	2.31	1.55	2.42	2.52	97	82
	A.J.	65	Cer. inf.	12 mg. t.i.d./7 d.	37	38	2.24	2.29	2.57	2.75	83	87
	H.G.	35	Epilepsy	18 mg. t.i.d./7 d.	74	59	1.15	1.39	3.46	2.56	85	82
	J.R.	67	Cer. inf.	18 mg. t.i.d./10 d.	50	66	2.02	1.35	2.17	2.73	101	89
	M.J.	61	Cer. inf.	10 mg. t.i.d./10 d.	55	57	2.02	1.88	4.44	4.50	111	107

T.L.	52	Cer. inf.	18 mg. t.i.d./8 d.	58	40	1.89	2.28	3.53	2.31	110	91
L.T.	73	Cer. inf.	12 mg. t.i.d./10 d.	44	43	3.32	3.56	3.45	2.73	146	153
Mean				48	52	2.22	1.97	3.16	3.28	102	96
Mean diff.				+4		−.25		+.12		−6	
S.L.	71	Cer. inf.	18 mg. t.i.d./23 d.	35	51	3.43	2.06	2.91	2.76	120	105
H.F.	45	Cer. isch.	18 mg. t.i.d./42 d.	40	51	3.40	2.71	2.60	4.29	136	138
R.P.	53	Cer. inf.	18 mg. t.i.d./19 d.	29	49	3.69	2.18	2.40	3.19	107	107
J.W.	60	Cer. inf.	18 mg. t.i.d./24 d.	29 / 42	47	3.59 / 2.29	1.96	2.27 / 2.27	2.59	104 / 96	92
R.W.	65	Cer. inf.	18 mg. t.i.d./26 d.	31 / 47	56	2.94 / 1.85	1.36	1.68 / 2.53	2.98	91 / 87	76
C.J.	64	Cer. inf.	18 mg. t.i.d./49 d.	53	68	2.30	2.04	3.53	3.25	122	139
J.W.	55	Cer. inf.	18 mg. t.i.d./24 d.	29	38	3.31	2.18	1.89	2.37	96	83
Mean				35	51	3.24	2.07	2.47	3.06	111	106
Mean diff.				+16		−1.17		+.59		−5	
p				<.001		<.01					

Group Receiving Drug for periods greater than 2 weeks

*Values obtained after nylidrin had been discontinued for 7 days.
Cer. inf.: Cerebral infarction
Diff. vas. dis.: Diffuse cerebral vascular disease without localizing manifestations.
Cer. isch.: Recurrent episodes of cerebral ischemia
C = control values.
Tr. = Values obtained following nylidrin therapy.

TABLE 2.—BLOOD CONSTITUENTS BEFORE AND AFTER THE ORAL ADMINISTRATION OF NYLIDRIN HYDROCHLORIDE (ARLIDIN)

	Subject	Arterial O_2 Content Vol. %		Venous Oxygen Content Vol. %		Arterio-venous O_2 Difference Vol. %		Arterial CO_2 Content Vol. %		Venous CO_2 Content Vol. %		Arterial pH		Arterial pCO_2 mm. Hg		Hematocrit mm. %	
		C	Tr.	C	Tr.	C	Tr.	C	Tr.	C	Tr.	C	Tr.	C	Tr.	C	Tr.
Group Receiving Drug for periods less then 2 weeks	G.R.	16.86	16.06	10.61	10.55	6.25	5.51	48.26	48.97	54.69	55.31	7.36	7.32	45	47	41	39
	G.B.	19.39	17.56	10.22	8.97	9.17	8.59	48.09	50.87	56.01	60.24	7.32	—	48	—	53	49
	O.C.	19.12	17.63	11.23	8.56	9.07	5.81	41.61	40.01	50.00	48.51	7.33	7.35	44	40	48	43
	C.C.H.	17.28	16.98	11.47	9.98	5.81	7.00	41.62	41.35	47.89	48.81	7.35	7.30	40	43	45	42
	A.D.	19.26	19.04	11.11	11.55	8.15	7.49	47.63	44.55	55.11	52.42	7.40	7.36	41	39	46	47
	L.S.	16.55	15.97	10.43	10.01	6.12	5.96	47.08	49.48	53.43	53.67	7.32	7.40	48	48	45	40
	G.J.	17.45 / 16.63*	15.93	9.13 / 8.10*	9.31	8.32 / 8.53*	6.62	47.31 / 47.99*	44.10	54.51 / 54.77*	52.53	7.35 / 7.36*	7.30	45 / 44*	47	48 / 42*	43
	H.E.	15.84 / 15.72*	15.13	10.34 / 8.77*	9.61	5.50 / 6.95*	5.52	47.92 / 48.33*	48.28	52.29 / 54.72*	55.16	7.33 / 7.35*	7.38	46 / 44*	42	40 / 37*	37
	J.Mc.	18.22	17.42	12.45	12.66	5.77	4.76	45.01	45.45	49.01	51.15	7.36	—	41	—	42	43
	A.J.	17.72	17.96	10.77	10.72	6.95	7.24	43.78	42.52	50.83	49.48	7.36	7.39	41	38	45	44
	H.G.	14.08	13.14	9.41	8.80	4.68	4.34	46.15	43.85	50.88	49.68	7.33	7.35	44	42	37	28
	J.R.	8.99	8.60	4.65	4.47	4.34	4.13	44.01	45.59	48.29	48.49	—	7.33	—	41	28	25
	M.J.	18.87	18.86	10.79	10.97	8.08	7.89	41.76	42.20	49.74	49.10	7.34	7.34	41	41	46	46

M.J.	18.87	18.86	10.79	10.97	8.08	7.89	41.76	42.20	49.74	49.10	7.34	7.34	41	41	46	46
T.L.	15.42	14.97	9.34	9.20	6.08	5.77	44.12	40.88	50.53	46.25	7.30	7.38	46	38	39	37
L.T.	15.95	15.56	8.11	9.21	7.84	6.35	45.86	44.11	53.70	48.52	7.35	7.38	43	39	42	39
Mean	16.73	16.05	10.00	9.58	6.72	6.41	45.35	44.81	51.79	51.29	7.34	7.35			43	41
Mean Diff.	−.68		−.42		−.31		−.54		−.50		+.01				−2	
p															<.01	
S.L.	17.23	16.05	8.93	10.64	8.30	5.41	43.72	47.85	50.71	52.25	7.35	7.30	41	50	40	39
H.F.	19.78	18.25	13.27	9.83	6.51	8.42	46.65	45.58	52.05	51.13	7.33	7.34	46	45	46	51
R.P.	17.40	15.30	9.11	8.84	8.29	6.51	38.76	42.21	48.28	47.66	7.31	—	41	—	45	41
J.W.	15.50 12.21*	13.10	7.67 6.81*	7.58	7.83 5.40*	5.52	35.63 40.51*	37.77	42.04 45.34*	43.05	7.33 7.35*	7.30	34 35*	38	38 31*	29
R.W.	14.51 14.34*	14.31	9.09 8.96*	8.99	5.42 5.38*	5.32	45.22 46.33*	45.19	50.19 51.20*	50.79	7.33 —	7.33	44 —	44	37 38*	37
C.J.	16.23	14.68	9.57	9.90	6.66	4.78	46.02	47.32	53.27	52.06	7.31	—	47	—	38	39
J.W.	16.81	15.64	10.28	9.41	6.53	6.23	46.28	47.86	53.70	54.51	7.37	7.35	42	43	40	39
Mean	16.78	15.33	9.70	9.31	7.08	6.03	43.18	44.18	50.03	50.21	7.33	7.32	44	44	41	39
Mean Diff.	−1.45		−.39		−1.05		+1.65		+.18		−.01				−2.0	

Group Receiving Drug for periods greater than 2 weeks

*Values obtained after nylidrin had been discontinued for 7 days.
C = control values
Tr. = Values obtained following nylidrin therapy.

patients' clinical status was considered to be fairly stable; this was done in an attempt to avoid spontaneous alterations in cerebral blood flow incident to clinical improvement or deterioration.

Following clinical evaluation of the patients and the correction of any existing fluid and electrolyte disorders, the initial measurements of cerebral blood flow and metabolism were made. Oral nylidrin administration was then begun; initially a dosage of 12 mg., 3 times daily, was employed; this was subsequently increased to 18 mg., 3 times daily. After a treatment period of 7 or more days, the measurements were repeated; 18 mg. of nylidrin was given 30 minutes prior to the second determination.

Cerebral blood flow (CBF) was measured by the nitrous oxide method of Kety and Schmidt[4], as modified by Scheinberg and Stead[6]. The analytical methods employed have been described in a previous publication (Sensenbach *et al.*[7]). Mean arterial blood pressure (MABP) was measured directly from a convenient artery by a damped mercury manometer. Cerebral vascular resistance (CVR) was calculated from the CBF and MABP, and cerebral metabolic rate of O_2 ($CMRO_2$) was derived from the arterial-cerebral venous oxygen difference. pCO_2 was calculated from the nomogram of Singer and Hastings[8].

Results. The results are presented in Tables 1 and 2. During the course of the study it became apparent that more consistent changes were obtained when the patients were treated for 2 weeks or longer. Therefore, the results of short-term (<2 weeks) and long-term (>2 weeks) therapy are analyzed separately.

In patients treated for less than 2 weeks the oral administration of nylidrin had a variable effect on CBF, although there was a tendency toward an increase. On the other hand, in 7 patients treated for longer periods there was a 43% increase in cerebral blood flow; this was a highly significant ($p<.001$) change. CVR was not significantly altered by treatment in the short-term group, but there was a significant decrease ($p<.01$) in resistance in the long-term group. Arterial-cerebral venous oxygen difference was not significantly altered by the drug, although a tendency toward a decrease is evident. $CMRO_2$ increased in 2/3 of all of the patients studied; this increase, however, was not statistically significant. MABP tended to decrease in both groups, but this was not a consistent effect. The hematocrit decreased slightly in almost every instance; although this minor change was significant in the larger group of patients, the nature of the study does not permit the conclusion that nylidrin administration induces significant alterations in red cell mass or plasma volume. Arterial pH was moderately decreased in several of the subjects, as were the values for CO_2 content. However, there were no consistent or significant changes following treatment. The low arterial oxygen content in some of the subjects reflected the presence of a mild to moderate anemia; there was no significant change in this parameter following nylidrin therapy.

Discussion. The results of this study indicate that the oral administration of nylidrin hydrochloride (Arlidin) was associated in most instances with an increase in cerebral blood flow. This increase in flow was accompanied by a decline in cerebral vascular resistance; MABP decreased in most instances but the increase in blood flow was apparently independent of this alteration. Cerebral metabolic rate for oxygen was increased in some but not all of the subjects.

Although low pH values of obscure cause were encountered sporadically, the increase in cerebral perfusion incident to nylidrin administration occurred in the absence of consistent changes in pCO_2 or pH, suggesting a primary cardiovascular effect of the drug. This could represent either a direct effect of Arlidin on cerebral blood vessels or could be due to an

increase in cardiac output. It has been suggested that nylidrin increases cardiac output (Caliva *et al.*[1]), perhaps contributing to the augmentation of peripheral as well as cerebral blood flow. However, this parameter was not actually measured and the mechanism whereby cerebral perfusion is increased under the influence of this agent is not clear.

The failure of nylidrin to induce significant vasodilatation in certain subjects may have been related to the severity of the vascular disease. Gorlin, Brachfeld, MacLeod and Bopp[2] have shown that coronary blood flow increases in normal subjects under the influence of nitroglycerine but that this does not occur in persons with angina pectoris. It is conceivable that a similar situation exists in patients with cerebral vascular disease and that severely sclerotic vessels are incapable of dilatation. On the other hand, there are few subjects in whom CO_2 administration will fail to effect significant cerebral vasodilatation.

It has not been clearly established that benefit accrues to the patient with cerebral vascular disease when blood flow to the brain is increased. The results of CO_2 administration in patients with recent cerebral infarctions have been largely disappointing (Wright and Luckey[9]), although occasional patients are apparently benefited. On the other hand, under certain circumstances effective cerebral vasodilatation might be distinctly advantageous. Thus, in persons with recurrent attacks of cerebral ischemia augmentation of cerebral blood flow might prevent these transient episodes or even ultimate infarction and might serve as a useful adjunct to anticoagulant therapy. In addition, where one or more cerebral infarctions have occurred, increasing cerebral blood flow might decrease the propensity to further thrombotic episodes. In the present study several of the patients seemingly improved during nylidrin therapy; thus, persons with recent cerebral infarctions with limited neurological deficits seemed to attain a clinical plateau more rapidly than untreated subjects. Whether or not a significant reduction in the extent of the infarct was effected could not be ascertained from this limited and uncontrolled investigation. There did emerge from this study the distinct impression that major functional deficits are not affected by increasing cerebral perfusion; thus, patients with longstanding hemiplegia and those with mental and personality changes without evidence of focal obliterative disease were not appreciably improved by treatment. Patients in the latter category, that is, those with "generalized cerebral arteriosclerosis," cannot be distinguished with certainty from subjects with senile cerebral atrophy, as cerebral blood flow is decreased in both circumstances; it may well be that the cerebral changes are primary in both instances and that atheromatous disease of the arterial tree plays a minor role in the genesis of this syndrome.

No apparent side effects of the drug were noted. In persons with angina pectoris 6-mg. doses were used initially; this was gradually increased to 18 mg., 3 times a day, without affecting the frequency or severity of anginal attacks. Patients who had had recent myocardial infarctions were excluded from the study. There were no apparent ill effects when the medication was abruptly discontinued.

Conclusions. 1. In persons with cerebral vascular disease the oral administration of nylidrin hydrochloride (Arlidin) for periods of greater than 2 weeks was associated with a 43% increase in cerebral blood flow. When given for shorter periods, this effect was inconsistent.

2. This increase in cerebral perfusion

was associated with a decrease in cerebral vascular resistance and, in many instances, a slight decline in mean arterial blood pressure.

3. As pH and pCO_2 were not significantly affected by nylidrin administration, a primary cardiovascular effect of the agent is suggested.

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SUMMARIO IN INTERLINGUA

Le Effecto de Hydrochloruro de Nylidrina (Arlidina) in le Circulation Cerebral

1. In subjectos con morbo cerebro-vascular, le administration oral de hydrochloruro de nylidrina (Arlidina) durante periodos de plus que 2 septimanas esseva associate con un augmento del fluxo de sanguine cerebral per 43%. Quando le droga esseva administrate durante minus extense periodos, le effecto non esseva uniforme.

2. Le augmento del perfusion cerebral esseva associate con un reduction del resistentia cerebro-vascular e, in multe casos, un leve declino del tension medie de sanguine arterial.

3. Viste que pH e pCO_2 non esseva afficite significativemente per le administration de nylidrina, un effecto cardiovascular primari del agente es suggerite.

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THE ABNORMAL HEMOGLOBINS

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THE abnormal hemoglobins have received much attention in recent years. To date, seventeen human hemoglobin variants have been identified by letter designations[97]. As more are discovered, it becomes increasingly difficult to keep pace with the investigators who are making such giant strides in this field. The purpose of this paper is to present a short comprehensive review of the abnormal hemoglobins, with stress upon general concepts. Those desiring more detailed information on specific aspects of this field, are referred to the many reviews published by the leading investigators[7,13,46,47,65,69,87,109,113].

Fetal hemoglobin was discovered in 1866. However, we did not become aware of the existence of abnormal hemoglobins and their relationship to hemolytic anemias until 1949, when sickle cell hemoglobin was identified by electrophoresis. The initial impetus leading to this discovery was supplied by Pauling and Castle in 1945, when they were called upon to serve on the Medical Advisory Committee that prepared the Bush Report. In the course of their discussions, Dr. Castle broached the subject of sickle cell anemia. He noted that sickling was prevented by oxygen and accelerated by carbon dioxide. The work of Hahn and Gillespie in 1927 had shown that sickling occurred only in the presence of a low partial pressure of oxygen[32]. These comments stimulated speculations. Dr. Pauling suggested that sickling must in some way involve the hemoglobin molecule. He suspected the difference between normal and

sickle erythrocytes to be the presence of an abnormal hemoglobin in the latter which, when deoxygenated, combined with itself, twisting the red blood cell out of shape[69]. This bud of suspicion unfolded in the full bloom of verification when Pauling and his collaborators subjected normal and sickle cell hemoglobin to electrophoresis. Since electrophoretic mobility is a function of chemical structure, the demonstration of the altered electrophoretic pattern of sickle cell hemoglobin proved the presence of an altered hemoglobin molecule. This work, published in 1949 under the title, "Sickle cell anemia—a molecular disease"[70], demonstrated beyond doubt that sickle cell anemia was associated with an abnormal hemoglobin. This contributed immeasurably to our knowledge of this entity and also introduced electrophoresis to the study of human hemoglobin.

The theoretical basis for electrophoresis lies in the fact that proteins are charged particles and can be made to move in an electrical field. The amount of charge assumed by the given protein and its resulting mobility is dependent upon the pH of the solution in which it is present. By varying the pH, the protein molecules can be made to move as negatively charged particles towards the anode, or in the opposite direction, as positively charged particles towards the cathode. At some point in between, a pH will be found at which net charge equals zero and no migration takes place. This is the isoelectric point. The isoelectric point will vary from one protein to another, and will be dependent on chemical structure and the total net charge resulting from the summation of the electrically active chemical components. Therefore, if we compare a number of different proteins in a medium of fixed pH, the differing mobilities will be a function of different isoelectric points, representing, in turn, different chemical structures. It is precisely these differences in isoelectric point and chemical structure that account for the different mobilities of the human hemoglobins in an aqueous solution of fixed pH, and enable us to distinguish one from another[47].

The natural consequence of the discovery of sickle cell hemoglobin was the beginning of the search for other abnormal hemoglobins, ushering in the so-called "modern era"[65] of the hemoglobinopathies. The search was intensified by the introduction of filter paper electrophoresis in 1953[95]. The substitution of this simple, inexpensive technique for the more complex Tiselius apparatus used initially, multiplied many-fold the number of laboratories that could now participate in the search. As a result, new abnormal hemoglobins were discovered at an increasingly more rapid rate after 1953.

Table 1 presents a list of the human hemoglobin variants discovered to date.

HEMOGLOBIN F. Fetal hemoglobin, or hemoglobin F, was identified in 1866 by von Korber[11]. He demonstrated that hemoglobin preparations of placental blood were more resistant to alkali denaturation than preparations of normal adult hemoglobin. This alkali-resistant hemoglobin was given the name fetal hemoglobin. In 1953, at the symposium that proposed the alphabet nomenclature for abnormal hemoglobins, it received the mnemonic designation of hemoglobin F[97]. On filter paper electrophoresis, hemoglobin F is virtually indistinguishable from normal adult hemoglobin (hemoglobin A). A convenient method for the quantitative measurement of hemoglobin F, based on its peculiar characteristic of alkali resistance, was developed by Singer and Chernoff in 1951[88].

TABLE 1.—ABNORMAL HEMOGLOBINS

Hgb	*Year Discovered*	*Investigators*	*Subjects in Whom Found*
F	1866	von Korber (discovered the alkali resistance of placental hemoglobin)	Found normally in the newborn. Found pathologically in a variety of congenital hemolytic anemias
S	1949	Pauling and Itano	Individuals with sickle cell anemia and trait
C	1950	Itano and Neel	American and African Negroes
D	1951	Itano	Widely dispersed incidence in Caucasians and Negroes
E	1954	Itano and Bergren	Orientals in South-East Asia
G	1954	Edington and Lehmann	Negroes in West Africa Also in an American family of Italian descent
H	1955	Rigas and Koler	Primarily in Orientals in association with thalassemia
I	1955	Rucknagel and Page	An American Negro family
J	1956	Thorup and Itano	American Negroes with isolated cases in Caucasians and Indonesians
K	1956	Cabannes	Berber tribesmen and East Indians
L	1957	Ager and Lehmann	An East Indian
M	1955	Singer	Individuals afflicted with hereditary methemoglobinemia
N	1958	Ager and Lehmann	African Negroes
O	1958	Lie-injo Luan Eng	Inhabitants of the Indonesian island of Sulawesi
P	1958	Schneider and Haggard	American Negro woman and child
Q	1958	Vella *et al.*	In a Chinese from Singapore

Normally this pigment is the predominant type found in the newborn. However, beginning at birth and possibly even during the last trimester of fetal development, there is a gradual replacement of fetal hemoglobin by adult hemoglobin, resulting in the disappearance of significant quantities of hemoglobin F within 6 to 24 months. Some hemoglobin F may persist even in the adult but does not normally exceed the range of 0.5% to 1.7% of the individual's total hemoglobin. High levels of hemoglobin F persisting in individuals beyond the age of 2 years is of pathological significance and can be found in a variety of anemias such as sickle cell anemia and thalassemia[88]. Its presence is thought by many to indicate a compensatory return to hemoglobin F production, triggered by the stress of a hemolytic process[109].

HEMOGLOBIN S. Sickled red cells are pathognomonic of hemoglobin S and are related to the decreased solubility of the reduced form of this hemoglobin. These cells were first observed as an isolated finding by Dresbach in 1904[24]. Their presence in association with severe anemia was described by Herrick in 1910 in the first clinical description of sickle cell anemia[34]. Initially called Herrick's anemia, it was thought to represent a variant of pernicious anemia. In 1915, Cook and Meyer reported the third case[20] and noted a familial incidence. They were the first to suggest that this was a new clinical entity. Mason, in describing the fourth case in 1922, coined the term sickle cell anemia[54]. Then, as the literature began to abound with clinical descriptions of this unusual anemia, attention was given to the factors producing sickling. It was the work of Hahn, Gillespie, and others that led to, and culminated in, the electrophoretic differentiation of hemoglobin S. Subsequently, Neel brought clarification to the genetic concepts involved[63, 64]. Extensive family studies revealed that the severe anemia associated with sickling occurred only when both parents possessed the sickling abnormality. He postulated that sickle cell anemia was the result of the inheritance of the sickle cell gene from both parents, the homozygous state. Sickling in the absence of severe anemia was presumed to be the manifestation of the heterozygous state and was termed sickle cell trait. A number of unusual cases ("sickle cell anemia" with sickling in only one parent) were found which seriously challenged this concept. The discovery of other abnormal hemoglobins soon provided a ready explanation.

Hemoglobin S is found almost exclusively in Negroes, although a number of cases have been described in Caucasians, especially those of Mediterranean extraction. Many surveys have been performed in this country and in Africa in an effort to determine the incidence of sickle cell hemoglobin. Composite results of these independent surveys were analyzed by Margolies and indicate a 9% incidence in the American Negro. Surveys in Africa showed considerable variation in incidence. The highest figures were obtained in areas of Central Africa where sickling was observed in 45% of the population[53].

HEMOGLOBIN C. Hemoglobin C was discovered in 1950[43]. It has been observed primarily in Negroes with very rare cases seen in Caucasians[23,36]. Surveys in Africa have shown this abnormality to occur with significant frequency in the Gold Coast where incidence figures range up to 20%[65]. Hemoglobin C occurs in 2 to 3% of American Negroes[80]. On filter paper electrophoresis in alkaline media, hemoglobin C exhibits the smallest amount of electrophoretic activity thus far observed in hemoglobin variants. The classical

hematological abnormality associated with hemoglobin C is target cell formation.

HEMOGLOBIN D. Hemoglobin D was initially described in 1951, in an American family of Irish, English, and American Indian descent[44]. While hemoglobins S and C are virtually confined to Negroes, surveys in search of hemoglobin D have indicated widely separated areas of incidence in different ethnic groups. In India, surveys revealed a 2% incidence[9], and in the American Negro, Chernoff established a 0.4% incidence[14]. Cases of hemoglobin D have been found in Algeria[71], and in the United States, in Americans of English ancestry[94]. It seems, thus far, to be one of the few abnormal hemoglobins that has successfully crossed racial borders. This prompted Chernoff to suggest that the genetic mutation responsible for hemoglobin D may have arisen independently in different portions of the world, rather than in one specific area[14].

The electrophoretic pattern of hemoglobin D is identical with that of hemoglobin S. It is distinguished from the latter by its normal solubility in the reduced form, and, consequently, the absence of sickling.

HEMOGLOBIN E. Hemoglobin E was identified in 1954 in an American family of Guatemalan, Spanish, and Hindu ancestry[45]. Subsequently, a large reservoir of this abnormal hemoglobin was found in Southeast Asia. Surveys in Thailand revealed a 12% incidence of this abnormality[59,60], and additional cases were found in Indonesia[27], Burma and Ceylon[5]. It has been noted frequently in association with thalassemia. (In recent years, thalassemia has been found to be quite prevalent in Southeast Asia[56].) On filter paper electrophoresis, hemoglobin E is intermediate in mobility to hemoglobins S and C. As in hemoglobin C syndromes, target cell formation is a virtually constant finding.

(No extensive surveys have been performed for the other hemoglobin variants, and our knowledge of them is still based, to a great extent, on isolated case reports.)

HEMOGLOBIN G. Hemoglobin G was initially noted in Negroes of West Africa[25]. Recently it has been described associated with hemoglobin S in an American family of Italian descent[83]. Curiously enough, the combination of hemoglobin G with hemoglobin S was asymptomatic, resembling a mere sickle cell trait. This is in contradistinction to the combinations of hemoglobin S with hemoglobins C or D which produce moderately severe, symptomatic anemias. This has led some observers to feel that hemoglobin G would be more accurately termed a normal variant rather than an abnormal hemoglobin. The fact that hemoglobin G produces no abnormality in the homozygous state[26] would tend to confirm this hypothesis. On filter paper electrophoresis, hemoglobin G is intermediate in mobility to hemoglobins S and A.

HEMOGLOBIN H. Hemoglobin H was described in 1955 in a Chinese family in association with thalassemia[76]. Practically all subsequent cases of this abnormality were similarly observed in orientals possessing also the thalassemia defect. Family studies of the index cases of hemoglobin H failed to reveal the abnormality in the parents[77]. Since the other hemoglobinopathies have been shown to be genetically determined, hemoglobin H is somewhat unique in this respect. A possible explanation is advanced by Motulsky who feels that the gene of hemoglobin H has poor penetrance and is not demonstrable in the pure trait form. In association with thalassemia, however, hemoglobin H is somehow acti-

vated, causing increased penetrance and clinical demonstrability[58]. Recently, Bingle *et al.* have reported cases that seriously challenge this concept. They observed pure hemoglobin H trait in two Greek Cypriots[8]. Further studies are necessary before a full understanding of the genetic characteristics of hemoglobin H is achieved. On filter paper electrophoresis, hemoglobin H demonstrates a greater mobility than hemoglobin A and was the first of the so-called "fast" hemoglobins.

HEMOGLOBIN I. This abnormality was identified in 1955 as an asymptomatic trait in an American Negro family[79]. On filter paper electrophoresis it was noted to have the mobility of hemoglobin H. Differentiation was accomplished with resin chromatography. With this method, hemoglobin I had a mobility greater than hemoglobin A but less than hemoglobin H. It is a rare type of hemoglobin and further information concerning this abnormality is not as yet available.

HEMOGLOBIN J. Hemoglobin J, the third of the "fast" hemoglobins, was described in 1956 in an American Negro family[104]. Additional examples of hemoglobin J were found in Indonesians[37], in a Gujerati Indian immigrated to Africa[75], and in an American of French-Canadian extraction[55]. On filter paper electrophoresis, hemoglobin J is intermediate between hemoglobin A and hemoglobins H and I.

HEMOGLOBIN K. Hemoglobin K was initially observed in three Berber families in North Africa[12]. In naming this hemoglobin, Cabannes encountered an unusual series of events. He initially named it hemoglobin I, unaware that this letter already had been used in naming the hemoglobin described by Rucknagel. He then reintroduced this variant in a subsequent publication with the name hemoglobin J, only to discover that Thorup and collaborators had described another new hemoglobin and had laid claims to the letter J[6]. This unfortunate state of affairs was eventually remedied at the Sixth Congress of the International Society of Hematology in 1956 when this variant was given the name Hemoglobin K[51]. Subsequent examples of this hemoglobin were found in two East Indians[1], and more recently a case was reported from Singapore[107]. It is a fourth "fast" hemoglobin with an electrophoretic mobility intermediate between hemoglobins A and J.

HEMOGLOBIN L. There has been only one reported case of hemoglobin L. It was found in 1957 in a Punjabi Hindu[2]. It is a "slow" hemoglobin, intermediate in electrophoretic mobility between hemoglobins S and G.

HEMOGLOBIN M. This variant represents the hemoglobin of congenital methemoglobinemia and has been subject to investigation for the past 50 years. In 1948, German investigators succeeded in splitting this hemoglobin molecule and recombining its globin portion with the heme from normal hemoglobin A. The absorption spectrum of methemoglobin was still present in the synthesized hemoglobin, and the abnormality was thereby localized to the globin moiety[35].

On filter paper electrophoresis, this hemoglobin migrates with hemoglobin A. However, three component bands can be identified, including a middle band of brownish coloration, representing the hemoglobin M portion. In the past year, separation of the A and M components was accomplished with starch block[30]. In 1955, Singer suggested that this hemoglobin with the designation hemoglobin M assume its place in the alphabet of hemoglobinopathies[87].

HEMOGLOBIN N. Considerable confusion attended the identification of hemoglobin N. In 1956, Robinson and

collaborators identified two "fast" hemoglobin components in Liberians[78]. They were provisionally named Liberian I and Liberian II. Initially, it was thought that they represented examples of hemoglobins J and K respectively. Certain incongruities cast doubt on the supposition that Liberian II was identical with hemoglobin K. As a consequence, the letter N was reserved for Liberian II until such time as it was demonstrated to be identical with, or differing from, Hemoglobin K. Ager and Lehmann[3] performed comparative studies on the hemoglobins in question and demonstrated that Liberian II and hemoglobin K were, in fact, identical. Subsequently, they received two other "fast" hemoglobin specimens obtained from West Africans. These were shown to be identical with Liberian I, and therefore, presumably, with hemoglobin J. However, studies comparing Liberian I and the two new specimens, with known specimens of hemoglobin J, indicated that they were faster than hemoglobin J and constituted a different type of hemoglobin. Consequently, the letter N, initially reserved for Liberian II, was applied instead to Liberian I and the new "fast" specimens from West Africa. Recently Trincao *et al.* reported 14 more cases of hemoglobin N found in Portuguese Guinea[105].

HEMOGLOBIN O. This abnormality, originally called "Buginese X," was recently confirmed as a new type of hemoglobin and given the designation of hemoglobin O[28]. It was identified in individuals from the Indonesian island of Sulawesi. Its electrophoretic mobility is intermediate between hemoglobins E and S.

HEMOGLOBIN P. This hemoglobin variant was observed in 1957 in an American Negro mother and child[81]. It was provisionally called the "Galveston" type. On filter paper electrophoresis, it is identical with hemoglobin L, holding a position intermediate between hemoglobins S and G. Differentiation from hemoglobin L and identification as a new type of hemoglobin were accomplished with resin chromatography in which they demonstrated differing mobilities[82].

HEMOGLOBIN Q. This abnormality was found in association with hemoglobin H in 1958 in a Chinese from Singapore[108]. Its electrophoretic mobility is less than that of hemoglobin A and slightly greater than hemoglobin G's.

A number of other hemoglobins such as "Norfolk's"[4], Hopkins I and Hopkins II[93], and two variants of fetal hemoglobin, "Bart's"[3], and "Alexandra"[29], are presently undergoing investigation. It can be expected that some, if not all, will soon receive distinctive letter designations.

Electrophoretic Patterns. With this preliminary introduction to the abnormal hemoglobins, we can proceed to further considerations concerning their electrophoretic differentiation. The simplest, most commonly used method of identification, is filter paper electrophoresis. The following is a short description of this method: A buffer solution of known pH is placed in an electrophoresis cell. Strips of filter paper are suspended in the cell so as to allow each end to come in contact with the buffer solution. After the buffer solution, through capillary action, has completely permeated the filter paper, hemoglobin specimens are centrally applied to the filter paper strips. An electrical current, transmitted through the paper by the buffer solution, causes the hemoglobin protein to migrate along the filter paper until it reaches the point of charge stabilization. After staining, the filter paper strips are ready for analysis, unknown being compared with simultaneously run known specimens.

The best separation of the human hemoglobins is obtained with a buffer solution of pH 8.6. At this alkaline pH, all human hemoglobins migrate as negatively charged particles towards the anode. Table 2 is a diagramatic representation of the mobilities of human hemoglobins in a barbital buffer of pH 8.6. It will be observed, that this method easily distinguishes the most commonly occurring hemoglobins: S, C, and A. Hemoglobin C demonstrates the least amount of mobility and, as one would expect, has an isoelectric point (pH 7.3) which most closely approaches that of the buffer solution. Hemoglobin A is isoelectric at pH 6.87. Hemoglobin S, intermediate in mobility between hemoglobin C and A, is also intermediate in isoelectric point (pH 7.09). The hemoglobins showing a mobility greater than hemoglobin A (hemoglobins H, I, J, K, and N) are referred to as the "fast" hemoglobins and are isoelectric at pH's of less than 6.87. The others (hemoglobins C, D, E, F, G, L, O, P, Q, and S) are called the "slow" hemoglobins. However, it should be stressed that the terms "fast" and "slow" are used only in a relative sense, and are descriptively applicable only when hemoglobin mobilities are compared in a buffer solution of alkaline pH. Analyzed in a buffer solution of pH 6.5, the hemoglobins will migrate in the opposite direction as positively charged particles towards the cathode. The "fast" hemoglobins now become "slow," and hemoglobin C, the "slowest" in an alkaline media because of its greater basic positivity, will now become the "fastest."

Paper electrophoresis has certain disadvantages. Among these are adsorption of the protein and unequal migration along the paper, producing the so-called "tailing" effect. These characteristics significantly compromise the efficacy of this method in distinguishing between hemoglobins of similar mobilities. As a consequence, methods utilizing other supporting media were devised. Kunkel, in 1955, employed a supporting medium of potato starch (starch block), and demonstrated three specific components in normal hemoglobin A: a main A_1 fraction, a "slow A_2 component, and a "fast" A_3[49,50]. Of particular interest is the finding of increased amounts of A_2 hemoglobin in patients with thalassemia[31].

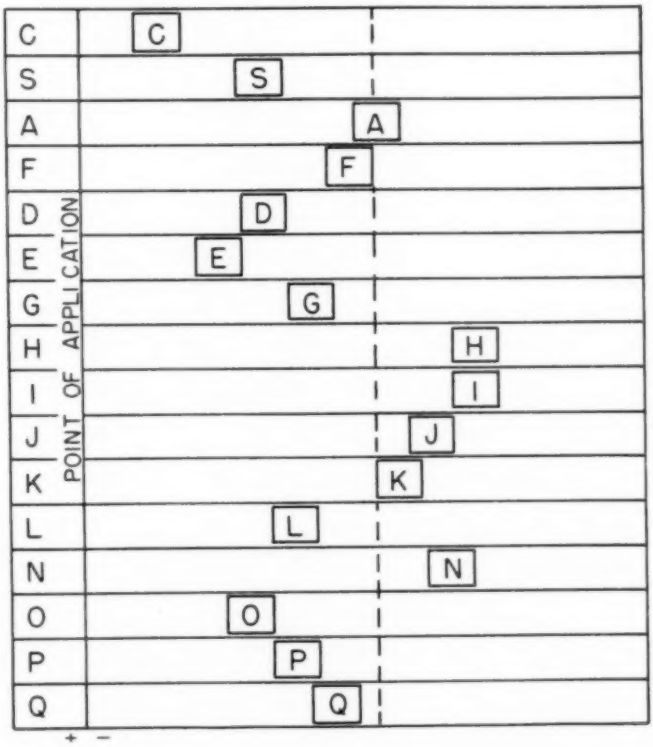
Resin chromatography, utilizing the cation exchange resin, Amberlite IRC 50, has also proved to be of considerable value[57]. Hemoglobins H and I, and hemoglobins L and P, indistinguishable on filter paper electrophoresis (Table 2) were identified successfully by resin chromatography. In addition, hemoglobins F and A, virtually indistinguishable on filter paper electrophoresis, are separated easily by chromatography. Huisman has stated that the utilization of both of these methods is important in establishing the identity of an abnormal hemoglobin[38]. These methods and others less widely used have been recently reviewed quite thoroughly by Beaven and Gratzer[7].

Clinical Manifestations. Hemolytic disease is related to two important factors: red cell production and destruction. Weinstein *et al.*, using radioactive chromium, demonstrated a shortened red cell survival time in sickle cell anemia and homozygous hemoglobin C disease[62,110]. With this increased blood destruction, a concomitant increase in blood production is necessary in order to maintain normal hemoglobin levels. Crosby and Ackeroyd have shown that the bone marrow has considerable reserve in its blood production capacity and can produce under stress, seven times the normal amount of hemoglobin[22]. Therefore, anemia should not result from merely increased

blood destruction unless survival time is reduced to less than 1/7th of normal (less than 15 to 20 days; normal, 120 days). However, in homozygous hemoglobin C disease, anemia was observed when the survival time was reduced to only 1/3 of normal (42 days)[103]. Thus, in addition to producing inferior types of hemoglobin, as evidenced by decreased survival times, these abnormal processes are also less efficient in erythrocyte production, and are unable to produce sufficient numbers to compensate for inferior quality. As a consequence, red cell production and destruction can be kept at equilibrium only by reducing total red cell mass to an anemic level. This, in general terms, is the mechanism by which anemia is produced in the abnormal hemoglobin diseases.

The abnormal hemoglobins occurring in the heterozygous state in combination with hemoglobin A, the "trait" form, are asymptomatic and cause no anemia, producing only hematological abnormalities such as sickling in hemoglobin S trait, and target cell formation in hemoglobin C and E traits. (Recently there have been case reports describing splenic infarction and hematuria in persons with sickle cell trait, indicating that this condition is not always asymptomatic[13].) In the homozygous state, however, anemia is produced ranging from the severe, dis-

TABLE 2.—ELECTROPHORETIC MOBILITY OF THE ABNORMAL HEMOGLOBINS IN A BARBITAL BUFFER OF pH 8.6



abling sickle cell anemia, to the benign, usually asymptomatic anemias associated with hemoglobin C[23,33,36,71,73,74,80,89,96,101,102,103,111], hemoglobin D[10,14,15], and hemoglobin E[17,52,61]. A notable exception is homozygous hemoglobin G "disease"[25,26,83], which as mentioned previously, causes no abnormalities whatsoever. Thus far, none of the other abnormal hemoglobins have been described in the homozygous state.

In addition, combinations of two different abnormal hemoglobins have been described. Hemoglobin S has been found interacting with hemoglobin C (SC disease)[48,68,73,80], and hemoglobin D (SD disease)[94,99,100]. These combinations, generally speaking, produce an anemia which is intermediate in severity to those produced by the respective homozygous states. Thus sickle cell-hemoglobin C (SC) disease is intermediate between sickle cell anemia and hemoglobin C disease, characterized by occasional hemolytic crises suggestive of sickle cell anemia, but with long intervals of benign, asymptomatic, mild anemia more typical of homozygous hemoglobin C disease. The same would obtain for sickle cell-hemoglobin D (SD) disease.

Thalassemia (Mediterranean or Cooley's anemia), another inherited form of hemolytic anemia, is most probably related to the abnormal hemoglobins. It was first described in 1925 as a severe, progressive, microcytic, hypochromic anemia with hepatosplenomegaly, commencing early in life and usually terminating fatally with an intercurrent infection[21]. Subsequently, it was noted that the parents of such an ill-fated child possessed erythrocytic abnormalities in the form of hypochromia, microcytosis, and varying degrees of anemia[114]. Initially called Cooley's anemia, Whipple introduced the term Mediterranean anemia, and then, thalassemia in 1936[112]. Valentine and Neel, in 1944, proposed a genetic theory of transmission[106]. Cooley's anemia was presumed to be the clinical expression of the homozygous state for a gene greatly altering erythrocyte synthesis, and was termed thalassemia major. The clinical syndrome found in the parents, representing the heterozygous state for this gene, was called thalassemia minor. Further studies, however, revealed the clinical manifestations of thalassemia to be quite variable, and the increasing number of "Mediterranean Hemolytic Disorders"[18] implied a concept of greater genetic complexity. Chernoff has postulated a scheme that includes three genetic factors controlling thalassemia: Factor A, an enzymatic defect responsible for the inability to incorporate iron in protoporphyrin; Factor B, producing abnormalities in red cell morphology; and Factor C, controlling hemoglobin F production. Utilizing this proposed scheme, thalassemia major becomes the homozygous state for all three factors (ABC/ABC), and thalassemia minor, the heterozygous state (ABC/abc). A number of combinations (ABc/abc—minimal thalassemia with no hemoglobin F/ aBC/abC, minimal thalassemia with high percentage of hemoglobin F/ and others) are now available to explain the clinical variability of thalassemia[16]. Nevertheless, the diagnosis of thalassemia remains one of inference. Aside from the inconstant finding of high percentages of hemoglobin F, no specific abnormal hemoglobin has been identified with thalassemia. Only after complete family studies and careful hematologic evaluation can this diagnosis be entertained.

More pertinent to our present discussion is the observed incidence of thalassemia in combination with a number of the abnormal hemoglobins

Sickle cell-thalassemia, or microdrepanocytic disease, was first noted in 1945 by Italian investigators[84,85]. Subsequently, cases were observed in the United States[67,72,91,92], and Greece[19]. The combination of the sickle cell and thalassemia abnormalities produces a clinical picture with the stigmata of both. There is a microcytic, hypochromic erythrocytosis and positive sickling. The hemoglobin is composed of type S and A with varying amounts of hemoglobin F. Clinically, although not as severe as either sickle cell anemia or thalassemia major, hemolytic crises, leg ulcers, hepatosplenomegaly, and severe anemia have been described. Thalassemia has also been found associated with hemoglobin C[90,92,115], and the unusual frequency of its association with hemoglobins E[17,61] and H[58,76,77] has already been mentioned. In addition, one case of hemoglobin D-thalassemia disease has already been reported[39]. In these latter abnormal hemoglobin-thalassemia diseases, the anemias produced are of only mild to moderate severity. On filter paper electrophoresis, the pattern observed is the same noted in the asymptomatic traits: namely, separation into two distinct bands, hemoglobin A and the abnormal hemoglobin. In the presence of thalassemia, however, the amount of abnormal hemoglobin is increased and the percentage of hemoglobin A is proportionally decreased. Consequently, in the abnormal hemoglobin-thalassemia disease, the abnormal hemoglobin predominates over hemoglobin A, while in the uncomplicated traits, hemoglobin A predominates. This constitutes further presumptive evidence that thalassemia somehow blocks the formation of hemoglobin A and, through this mechanism, enhances the expressivity of the abnormal gene.

The list of different anemias caused by the hemoglobinopathies is a formidable one. In Table 3, they are classified in order of severity for further clarification.

Genetic Concepts. The abnormal hemoglobins are genetically determined and transmitted according to the laws of Mendelian genetics as incomplete dominants[65,66]. Those that have been studied in detail, or have been noted in combination one with another, are allelomorphic: namely, interchangeable, expressed at the same locus on the same chromosome. Figure 1 illustrates the possible combinations resulting from various unions involving allelomorphic hemoglobins.

When abnormal hemoglobin-thalassemia diseases were observed, evidence was found indicating the presence of more than one genetic locus determining hemoglobin formation. Initially it was felt that thalassemia was allelomorphic with the abnormal hemoglobins[69]. If such were the case, the union of an individual with sickle cell-thalassemia and a normal would result in only two possible combinations in the offspring, either sickle cell trait or thalassemia minor. However, in 1952, Silvestroni reported a case of sickle cell-thalassemia in a child born to a man with sickle cell-thalassemia and his normal wife (Fig. 2). In a second family, the union of sickle cell-thalassemia and thalassemia minor resulted in a completely normal child[86]. Finally, Singer reported the birth of a normal child to a woman with hemoglobin C-thalassemia disease[90]. This was definite evidence that the thalassemia gene was not allelomorphic with hemoglobins S or C, and represented a second genetic locus governing hemoglobin formation.

The demonstration of more than one genetic locus determining hemoglobin formation called for a change in genetic symbols that would express all the dif-

TABLE 3.—THE ABNORMAL HEMOGLOBIN DISEASES IN APPROXIMATE ORDER OF SEVERITY

Thalassemia Major	Severe anemias, shortening
Sickle Cell Anemia	longevity
SD disease	Moderately severe
S-thalassemia disease	symptomatic anemias
SC disease	
E-thalassemia disease	
H-thalassemia disease	
C-thalassemia disease	
Hemoglobin C disease	Mild, usually asymptomatic
Hemoglobin E disease	anemias
Hemoglobin D disease	
Thalassemia Minor	
Sickle Cell trait	Sickling
Hemoglobin C trait	Target cell formation
Hemoglobin E trait	
Hemoglobin G "disease"	No abnormalities

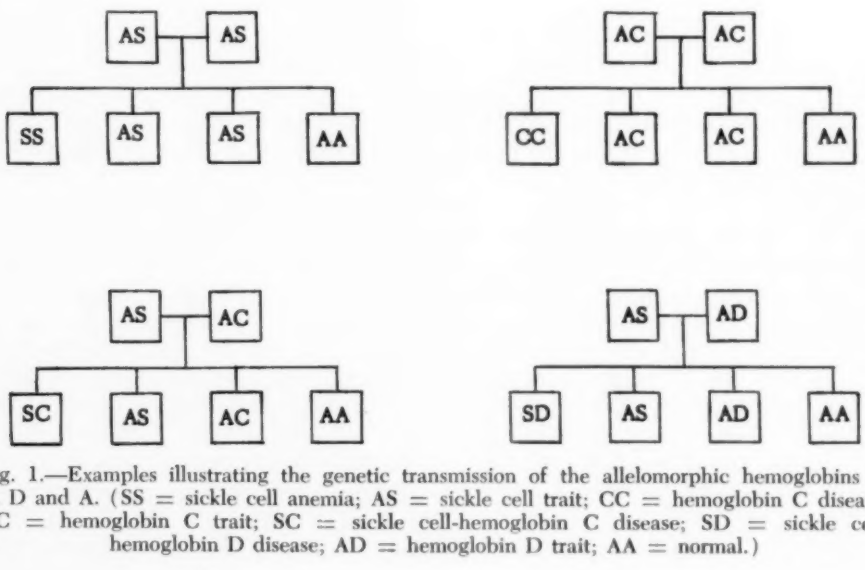


Fig. 1.—Examples illustrating the genetic transmission of the allelomorphic hemoglobins S, C, D and A. (SS = sickle cell anemia; AS = sickle cell trait; CC = hemoglobin C disease; AC = hemoglobin C trait; SC = sickle cell-hemoglobin C disease; SD = sickle cell-hemoglobin D disease; AD = hemoglobin D trait; AA = normal.)

ferent loci. Neel submitted in 1956 a new genetic nomenclature which was accepted, with some modification, by the Sixth Congress of the International Society of Hematology[66]. The first genetic locus determining hemoglobin formation was given the symbol Hb_1. The allelomorphic genes proven to occur at that locus (the normal A gene and the abnormal genes S and C) were given the symbols Hb_1^A, Hb_1^S, and *et al.*[83] in their report of hemoglobin S, hemoglobin G, and thalassemia in one family, indicates that hemoglobin G is not allelomorphic with either hemoglobin S or thalassemia, and is determined at yet another genetic locus governing hemoglobin formation. This locus has been called Hb_2. The only genes shown to occur at this locus are Hb_2^G and its normal allele, Hb_2^A. Sufficient evidence is not as yet available

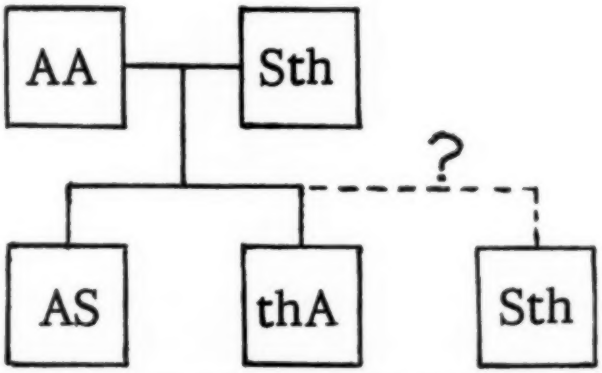


Fig. 2.—Schematic genetic representation of the union of an individual with sickle cell-thalassemia with a normal subject, where sickle cell hemoglobin and thalassemia defect are represented as allelomorphic: unexplained occurrence of sickle cell-thalassemia in one of the offspring as reported by Silvestroni[86]. (Sth = sickle cell-thalassemia.)

Hb_1^C respectively. The thalassemia locus was termed Th with the thalassemia gene represented by Th^T and the normal allele Th^N. Utilizing this terminology, sickle cell-thalassemia becomes the simultaneous presence in one individual of both sickle cell trait and thalassemia minor—Hb_1^S Hb_1^A/Th^T Th^N. The normal genotype would be expressed Hb_1^A Hb_1^A/Th^N Th^N. In Fig. 3, using these genetic symbols representing different genetic loci for sickle cell hemoglobin and thalassemia, we have explained the occurrence of a sickle cell-thalassemia offspring in the first family reported by Silvestroni (Fig. 2).

Evidence brought forth by Schwartz to determine the genetic relationship of the other abnormal hemoglobins to those already described. Should such evidence become available, even more genetic loci governing hemoglobin formation may be identified.

Biochemical Aspects. The success achieved with electrophoresis in the study of the abnormal hemoglobins indicates that an altered chemical structure is their underlying defect. As a consequence, a number of investigators attempted microanalytic studies of the amino acid composition of the human hemoglobins[98]. Studies performed by Huisman revealed that the amino acid composition of fetal hemoglobin differed markedly from that of the adult

hemoglobins. However, the amino acid composition of the adult hemoglobins was found to be remarkably similar[36]. A major breakthrough was accomplished by Ingram in 1957, when he described the chemical difference between normal and sickle cell hemoglobin[40].

The large size of the hemoglobin molecule greatly hampered efforts to determine the amino acid composition. electrophoresis and paper chromatography, spreading the peptide spots in a characteristic map or "fingerprint." Under special conditions, they were able to obtain "fingerprints" of hemoglobins S and A, in which all peptides occupied identical positions except for one, the peptide No. 4. Hemoglobin C was subjected to a similar process and again, the only "fingerprint" alteration was noted at peptide No. 4[41].

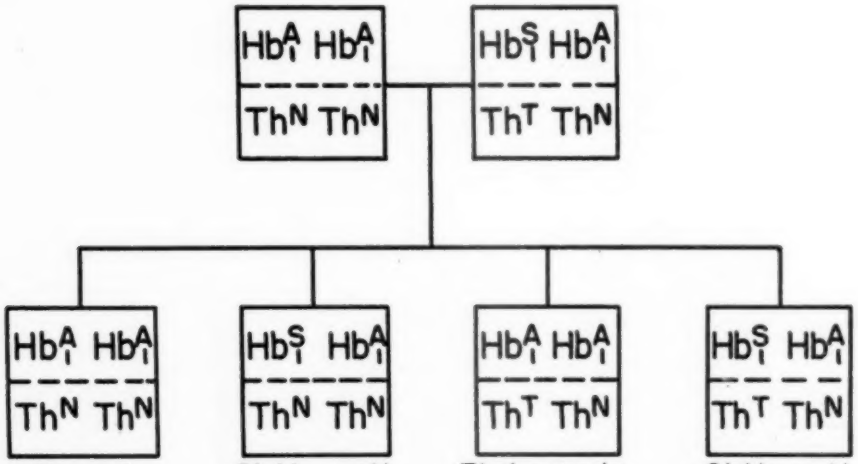


Fig. 3.—Genetic representation of the union of sickle cell-thalassemia with a normal, utilizing the genetic nomenclature adopted at the Sixth Congress of the International Society of Hematology, and indicating different genetic loci for sickle cell hemoglobin and thalassemia defect. The occurrence of sickle cell-thalassemia in one of the offspring is now explained.

In 1956, Ingram began experiments aimed at the degradation of the hemoglobin molecule into smaller peptide fragments. Success was finally achieved with trypsin which transformed the hemoglobin molecule into a mixture of approximately twenty-five different peptide chains, composed of nine or ten amino acids each. Subsequently, the tryptic digests of hemoglobin S and hemoglobin A were compared by a two dimensional combination of paper

In view of these findings, it was concluded that the only site of chemical alteration was located at the peptides No. 4 of these three hemoglobins. Identification of the amino acid structure of the other peptide spots confirmed the absence of chemical differences at other locations. Table 4 shows the amino acid structure of the peptides No. 4 of hemoglobins A, S, and C. Each of the peptides No. 4 is composed of nine amino acids. They are prac-

tically identical, differing in only one amino acid constituent. The number seven glutamic acid in hemoglobin A is replaced by valine in hemoglobin S, and lysine in hemoglobin C. Therefore, hemoglobins S and C differ from hemoglobin A in only one of 300 amino acids[42].

"slowest," must have, therefore, the least negativity. In hemoglobin C, a negatively charged glutamic acid is replaced by a positively charged lysine molecule. As a result, hemoglobin C has two less negative charges than hemoglobin A: the one replaced, and the one neutralized by the added lysine molecule. Hemoglobin S, intermediate in motility, has lost only one negative charge since valine is a neutral amino acid.

TABLE 4.—THE AMINO ACID COMPOSITION OF THE PEPTIDES NO. 4

Hemoglobin A	*Hemoglobin S*	*Hemoglobin C*
Histidine	Histidine	Histidine
Valine	Valine	Valine
Leucine	Leucine	Leucine
Leucine	Leucine	Leucine
Threonine	Threonine	Threonine
Proline	Proline	Proline
Glutamic acid	Valine	Lysine
Glutamic acid	Glutamic acid	Glutamic acid
Lysine	Lysine	Lysine

This difference, as small as it may be, possibly explains the difference in electrophoretic mobility shown by these three hemoglobins. It will be recalled that, at an alkaline pH at which all hemoglobins migrate as negatively charged particles, hemoglobin A showed greater mobility than either hemoglobin S or hemoglobin C. Consequently, of the three, it has the greatest net negativity. Hemoglobin C, the

Summary. A short, comprehensive review of the abnormal hemoglobins has been attempted. An abundance of detail has been deliberately avoided in order to focus most attention upon the "forest," and avoid becoming lost among "trees" of controversy.

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NEUROLOGY AND PSYCHIATRY

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THE ARTERIOLE IN NEURAL LESIONS

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ARTERIAL diseases which affect the nervous system rank high among man's killers[27]. Of these diseases, necrotizing arteriolitis, hypertensive arteriolosclerosis and atherosclerosis are also a major cause of morbidity. Its magnitude lessens the significance of current longevity statistics. Many of those living longer are ineffective as a result of vascular lesions of the brain. Longevity will have meaning after the cerebrospinal ravages of vascular disease are preventable. Vasculitis of the neuron denervates important systems and structures. The master functions of integration may be destroyed. Defective cardiac output and large vessel obstruction, extraneural vascular lesions, may contribute to nervous system destruction.

Attack on vascular disease of the nervous system has revealed fragmentary information on the multiple pathogenetic mechanisms. The treatment is restricted to relief of symptoms. Prevention, as yet, can only be discussed empirically.

A perspective of vascular diseases may be obtained by considering its current significance in relation to its background. Historical knowledge of the circulation indicates that for many years interest was confined to the larger vessels and heart. Modern medicine began in the Italian Renaissance about 1500 A.D. During the last five centuries medical art has struggled to achieve a refinement of understanding of the circulation. Advances of note have led from gross to microscopic anatomy and pathology. This path has progressed from the heart, the pulmonary vessels, the larger systemic arteries and veins, to the arteriolar-capillary beds, especially those about the visceral cells. Recently there has been increasing interest in physiologic factors operating in disease of the arteriole. The physiologically important vascular ramparts about cells of the brain are deserving of comment. Ischemia and anoxia of brain cells result in immediate dysfunction and then necrosis. This is appreciated in the cerebral arteriolar flow insufficiency of shock and cardiac asystole. A continuous supply of oxygen and glucose is required by brain cells. They do not store glucose and

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cannot utilize oxygen except through the oxidation of glucose. The importance of arteriolar function to cells is a more recent concept. This has developed largely as a result of observations on human cerebral function.

From Galen[19] to Leonardo, a period of 14 centuries, only animal dissection was practiced. In the early Renaissance, Leonardo[40] dramatized human observation and dissection in art. He thereby opened a new epoch in medicine. Leonardo's contribution, not yet fully appreciated, should have established permanently the value of human observation. Nevertheless, human science was partially emancipated from the political backwardness and stasis of the dark ages. The upgrading of medical science by Leonardo, painter of the Last Supper, was a harmonic overtone of the surging pressures of 15 centuries of Christian ethics surmounting its bonds.

In 1543 Vesalius[59] of Padua published the first system of human anatomy. Osler[41] and Cushing[11] have called this the greatest medical book written. Ten years later Servetus[55] published the first fundamental discovery of respiratory and circulatory physiology describing the pulmonary circulation. He saw blood as a medium moving from the right heart to the lung and back through the pulmonary veins to the left heart. Servetus' observations acclaim the eye as a great instrument in medicine. In 1600 Harvey[33] described the systemic circulation, roughly quantitating cardiac output and circulatory volume. His experiments demonstrated that blood pumped from the left heart flowed through the systemic arteries to the organs and to the periphery of the extremities, returning through the veins to the right heart. Servetus and Harvey assumed the existence of the arteriolar-capillary systems, but these were beyond the unaided vision. With the aid of Von Leeuwenhoek's microscope, Malpighi[16] (DePulmonibus, 1661) pictured the arteriolar-capillary flow in the lung and viscera.

Two centuries after Servetus, Priestly[26] in 1774, opened the lock-box of pulmonary alveolar vascular physiology by his discoveries of oxygen and carbon dioxide. He related oxygen, which he called pure air, to inspiration, florid blood, and biologic oxidation and heat production. He experimented with fermenting beer, isolating CO_2. Later he identified this gas as the respiratory principle of exhaled air. Priestly communicated his concepts to Lavoisier who gave to "pure air" the name of oxygen. Lavoisier[17] set forth respiratory physiology in simple terms. Oxygen inspired into the pulmonary air sacs, passed into the pulmonary capillaries and saturated the venous blood, replacing carbon dioxide. The oxygenated blood then returned through the pulmonary veins to the left heart. On ventricular contraction the florid oxygenated blood then was forced into the systemic circulation. There in the arteriolar-capillary beds oxygen was exchanged to the cells for carbon dioxide. The unsaturated venous blood then returned to the right heart and the pulmonary arteriolar-capillary beds in which CO_2 was exchanged through the air sacs.

Current interpretation suggests that two arteriolar-capillary beds, one for oxygen uptake and the other for oxygen delivery to the cell, stand between man's environment and his visceral cells. In arteriolitis, brain cell oxygen exchange may be affected in one or both arteriolar-capillary systems. Classical periarteritis nodosa attacks the systemic including the bronchial arterioles, but not the pulmonary beds with the following exception: in pulmonary hypertension the pulmonary circulation and arterioles are commonly af-

fected. This is also true in atherosclerosis.

The reasons for pulmonary arteriolitis as a result of pulmonary hypertension have not been completely clarified. Symmers[57] stated, "Hypertension appears to be the major etiologic factor responsible for polyarteritis nodosa-like lesions which may be found limited to the pulmonary arterioles, in cases of pulmonary hypertension." Rose and Spencer[50] have divided periarteritis nodosa into two types, with and without pulmonary arteritis.

Malpighi's great microscopic observations on "fixed" arterioles were animated two centuries later by direct visualization of living arterioles. Invention of the ophthalmoscope in 1850 by von Helmholtz[62] empowered von Graefe[61] to observe papilledema (Stauungspapille) and subsequent optic atrophy. Arteriolar occlusion was first seen as a dynamic process in the central arteriole of the retina by von Graefe. Virchow, a founder of cellular pathology, then described microscopically these vascular changes in fixed tissues. Allbutt[1] coined the term choked disc. He described albuminuric retinitis. These contributions aided in the development of Allbutt's concept of the entity of hypertension. Gowers[22] in 1890 described a case of "albuminuric retinitis" in a hemiplegic patient without albuminuria, a case of malignant hypertension. In 1896 Riva Rocci[49] developed the sphygmomanometer. This has aided in differentiating the hypertensions with abnormal diastolic, systolic, and pulse pressures.

In 1853, three years after Helmholtz's invention of the ophthalmoscope, Charcot[4,5] at the Salpetriere began a series of observations on the relation of neural, joint, and cardiovascular lesions. After writing a thesis on rheumatism, Charcot differentiated gout from rheumatoid arthritis. He remarked that the cardiac lesions of rheumatoid arthritis were similar in character but lesser in degree than those of acute articular rheumatism. He then conceived the pathogenesis of neurotrophic arthropathy in tabetic atrophy of dorso-spinal syphilis. This arthropathy is referred to as Charcot's joint. Charcot depicted destruction of bone and cartilage associated with incomplete bony repair as a late characteristic of tabetic neurotrophic arthropathy. The destruction may be comparatively painless. The multiple pathogenetic mechanisms in Charcot joint have not been discerned. It has not been reproduced experimentally. The Charcot joint occurs in syringomyelia, acromegaly, and diabetic pseudotabes, noninfectious diseases of the spinal cord. The neurologic lesion is basic to the development of neurotrophic arthropathy. Present knowledge suggests a vascular contribution in the pathogenesis of the neurologic lesion. The occasional rapid onset of the clinical arthropathy favors this concept. Charcot's classical clinical descriptions of joint and neural lesions affecting the extremities were complimented by his understanding of ischemia. He recognized and described intermittent claudication in man as a painful paralysis of ischemic origin. Charcot differentiated midline and contralateral decubitus as trophic neurovascular lesions of spinal and cerebral origin respectively. He emphasized that cerebral hemorrhage was commonly caused by aneurysms resulting from arteritis.

Pierre Marie[42,43] an associate of Charcot's, described acromegaly. This macrosomia, resulting from tumor of the anterior pituitary growth cells, is recognized by the facies and enlargement of terminal body parts and long bones. In acromegaly, the neurotrophic joint of Charcot also occurs. The final stages of the Charcot

joint in tabes dorsalis and acromegaly are the same. However, the pathogenesis probably involves the operation of common factors. In acromegaly there is foraminal compression of neural roots hypertrophied from hormonal overgrowth. Glial hypertrophy beyond the foramen also compresses neural fibers. In the presence of these compressions radicular and neural circulation is likely embarrassed. Pierre Marie was aware of acromegalic sclerotic overgrowth of the arteriole. He drew a sclerotic arteriole from the vasa nervorum of the stellate sympathetic ganglion. The extent of the increased incidence of Charcot joint in acromegaly as a result of acromegalic diabetes mellitus is unknown.

From the digital hypertrophy of acromegaly, Pierre Marie was able to differentiate a superficially similar entity which he termed chronic pulmonary hypertrophic osteoarthropathy. This he associated with cardiopulmonary lesions, especially sepsis and malignancy. Cyanosis of the hypertrophied terminal phalanges would suggest ischemia as one of the factors operating in the production of the osteoarthropathy. The observations of Charcot and Pierre Marie enlighten the neural, vascular, and joint relationships in many diseases.

In 1865 Kussmaul and Maier[37] gave the name of "periarteritis nodosa" to "a peculiar previously undescribed arterial disease associated with Bright's disease and rapidly developing generalized paralysis." Examination postmortem revealed characteristic changes in muscular arteries varying in size from that of the hepatic artery to microscopic arterioles. Nodules and aneurysms of inflammatory character suggested the name of periarteritis nodosa. Suggestions that Kussmaul's term "periarteritis nodosa" be changed to polyarteritis nodosa are not apropos. From a clinical point of view, Kussmaul correctly pointed out that arteriolitis or arteriolar dysfunction should be considered when polyneuritis is associated with a renal lesion.

From 1865 to 1900 a number of authors as remarked by Lamb[38], including Chvostek[8], Graf[23], Schmorl[53], and Verse[58], suggested that lues was the cause of periarteritis nodosa. This view was not held by Kussmaul, an astute observer of vascular and respiratory disease. Kussmaul identified diabetic coma and recognized it as an acidotic state by its classical hyperpnea; hence "Kussmaul's respiration." Other authors believed that periarteritis nodosa was an infectious disease, but bacteriologic investigation has remained unsubstantiating. It is of interest that in this period mercury and iodides, potentially sensitizing drugs, were used to treat lues and other diseases. Herxheimer[24] in 1902 described an erythematous inflammatory reaction of cutaneous syphilids, induced within hours after a patient's first mercurial inunction. On microscopic examination arteriolar reaction was apparent. Herxheimer[25] later stated that the reaction was not always specific for syphilis and was probably similar to the tuberculin reaction. The Herxheimer phenomenon does not occur during the natural course of syphilis. The Herxheimer phenomenon should be interpreted as a vascular reaction to therapeutic agents. It is of related interest that Rich[48] has reported the development of periarteritis nodosa as a hypersensitivity to iodides during the treatment of hyperthyroidism in nonluetic patients. Necrotizing vasculitis has been reported as a hypersensitivity to many agents including sulfonamides, arsenicals, antibiotics, vaccines, serums, and others.

In 1926 Von Glahn and Pappenheimer[60] described a "specific arteritis"

in rheumatism. Klinge[35] in 1930 and other German investigators suggested that antigenic reactions appeared to be a factor in the pathogenesis of rheumatic arteritis. Klinge and Vaubel[36] in 1931 suggested that rheumatic arteritis in severe cases may be related to periarteritis nodosa and in chronic cases may be a factor in the pathogenesis of arteriosclerosis. These authors examined the postulate that bacterial toxins, bacterial breakdown proteins, and therapeutic agents evoked antigen-antibody or hypersensitivity reactions. For some years it has been believed that the arteriolar wall participates in these reactions. The subsequent development of arteritis suggests a causal-effect relationship. Allergic factors in the pathogenesis of vasculitis have been questioned. Altshuler and Angevine[2] and Duff[12] have postulated that the characteristic pathologic change of fibrinoid necrosis is probably a nonspecific reaction of connective tissue to injury rather than an allergy. Nevertheless, it should be pointed out that many types of injury may result in the development of allergy or hypersensitization.

After overexposure to physical agents resulting in frostbite, sunburn, and immersion foot, forms of localized vasculitis and necrosis, hypersensitization to the original agent develops. Adrenalin may produce hypersensitive arteriolar spasm and necrosis in the foot of the sympathectomized extremity. Allergic symptoms are common in the history of patients with necrotizing vasculitis. Clinical understanding of various pathogenetic factors in vascular lesions is meager. This is true in hypertensive arteriolosclerosis and atherosclerosis as well as necrotizing arteriolitis. Our primary interest here concerns inflammatory and necrotizing processes affecting largely the arterioles and their functions. This lesion is herein referred to as necrotizing vasculitis. Zeek[66,67] has suggested the term "necrotizing angiitis" for lesions of unknown etiology in which arteries or veins of all sizes and in any location display inflammatory reaction and fibrinoid necrosis.

The term necrotizing vasculitis implies cellular dysfunction and necrosis secondary to arteriolar abnormality. The characteristic mural alterations of the arteriole include nodules, cylindrically thickened walls, medial dissolutions, and aneurysms. These changes may occur at vascular bifurcations. The major physiologic correlates of morphologic alterations are ischemia, anoxia, infarction, and hemorrhage. The pathologic processes of inflammation and fibrinoid necrosis underlie the morphologic and physiologic changes in arterioles and perivascular areas. Necrotizing vasculitis may be produced as a result of the operation of some of the following: susceptibility, infection, reinfection, immunization and hyperimmunity, hypersensitivity, chemical and physical agent exposure, drug sensitization, and unknown factors.

Factors in disseminate necrotizing vasculitis may also be a pathogenetic agent in other vascular lesions as hypertensive arteriolosclerosis, atherosclerosis, and arteriosclerosis obliterans. One constellation of physiologic factors common to the development of arteriolar lesions is that arterioles function in all viscera, are neurohumorally controlled, have muscular walls, and are regulatory of capillary flow. In view of these factors, consideration must be given to the effects of multiple system disease, neurohumorally controlled muscle spasm and hypertension, muscle disease and insufficient capillary flow. Disease of large arteries can hardly escape these considerations since arterioles are the blood supply of such arterial vessels as the aorta and its

branches. The vasa vasorum of the aorta do not originate from the aorta but from branches of the thoracic and lumbar arteries. Essential mechanisms of homeostasis and defense believed to be supported by the arteriole and its neurohumoral controls include participation in the reactions of temperature regulation, fluid balance, oxidation, inflammation, immunity, and toxemia. These mechanisms support cellular integrity. Although there is much uniformity of arteriolar function, visceral specialization produces differences.

Arterioles of the pulmonary system transport deoxygenated blood and are subjected to different pressures. Intraocular pressure partially neutralizes retinal-arteriolar pressure. In syncope loss of vision may precede loss of consciousness. Normally all visual functions are sustained by the retinal arteriolar system. In disseminate arteriolitis where physiologic factors contribute etiologically, it may be assumed that arterioles the size of those of the retinal system would be affected. Arterioles appear to be affected whether the arteriole stands alone or is part of the vasa vasorum system of larger vessels.

Historical review indicates that arteriolar functions merit increased attention in the pathogenesis of many diseases. The causes of arteriolitis, arteritis and rheumatism are unknown, although mechanisms previously listed are considered etiologically important. In a discussion of necrotizing vasculitis and necrotizing angiitis the following additional syndromes may be considered.

INFECTION. The clinical entities of necrotizing angiitis of infectious origin include those of tuberculosis, syphilis, and pyogenic organisms. A pyogenic infection of interest is subacute bacterial endocarditis. It occurs often in patients who previously have had rheumatic fever.

COLLAGEN DISORDERS. Necrotizing vasculitis may occur in any of the collagen disorders; for example, classical periarteritis nodosa, lupus erythematosus disseminatus, scleroderma, dermatomyositis, and rheumatoid arthritis. In "untreated" rheumatoid arthritis necrotizing vasculitis has been reported rarely. Arteriolar vasculitis indistinguishable from periarteritis nodosa has been reported by several investigators[31] in long term steroid-treated rheumatoid arthritis. "Therapeutic" vasculitis has been related by the author to hypersensitivity and therapeutic reactions as the tuberculin reaction, the Herxheimer phenomenon, therapeutic shock, and therapeutic paradox[28]. These reactions may be immediate or delayed, focal or generalized, or potentially fatal. The polyneuropathies of immunizations, diphtheritic and other post-infectious states, drug sensitizations, and the Landry-Guillain-Barre syndromes have been related to hypersensitivity vascular reactions. The ascending polyneuropathy associated with focal malignant neoplasm often can not be differentiated (clinically) from the Landry-Guillain-Barre syndrome.

HYPERSENSITIVITY ANGIITIS[67]. This is an acute necrotizing inflammation of small blood vessels frequently precipitated by the administration of a therapeutic agent for an infection. In contrast to periarteritis nodosa, hypersensitivity angiitis affects the pulmonary vessels frequently and the intestinal vessels rarely. Death may occur within a month. In surviving patients cerebral, cardiac, and renal damage are common.

DIABETES MELLITUS. This complex of vascular, metabolic, and other dysfunctions has been related to various lesions of the nervous system. These include neuropathies, cerebrovascular disease, and spinal cord syndromes. The 3rd, 6th, and 7th cranial nerves are occasionally affected. Peripherally the sciatic and femoral nerves are com-

monly affected. Initial complaints are pain and paresthesia. Anatomically the peripheral neuropathy is predominately an affection of the lower extremities. The relative severity of lower extremity involvement is in contrast to the neuritis of periarteritis nodosa. Sensory deficit is usually symmetrical. The motor neuropathy may be mononeuritic or polyneuritic and asymmetric. The frequency of unrecognized diabetes indicates that disease of the peripheral nerve merits thorough clinical consideration. "Amyotrophy" has been noted. Pseudotabetic syndromes with lancinating pains, A-R pupils, areflexia, ataxia, sphincter dysfunction, and Charcot joint may occur.

The neural syndromes may precede or follow the development of clinical diabetes mellitus. In the prediabetic state glycosuria is absent and fasting blood sugar determinations are normal. These therefore may not be helpful in diagnosing prediabetic neural lesions; a glucose tolerance test is necessary. The neural abnormality and insulin insufficiency high postprandial blood sugar do not correlate in degree. They may be symptomatic of different underlying disorders. Changes in the nervous system in the prediabetic patient may result from a vascular, or metabolic component, or both. Sullivan[56] has concluded that the asymmetric, painful, predominately motor neuropathy may be a result of arteriolar vasoneuropathy while the symmetric, distal, predominately sensory neuropathy may be a metabolic disorder. Ophthalmoscopic examination of the retinal arteriole suggests that vascular disease is an integral part of the diabetic state. The frequent association of diabetes with hypertension, atherosclerosis, arteriosclerosis obliterans, and the Kimmelstiel-Wilson syndrome also favors this belief. The neural manifestations are often independent of "diabetic control"[13]. Insulin is not a therapeutic agent for this neuritis. However insulin is related to oxygen and glucose utilization by neural cells. Neurologic and medical management must be circumspect and directed to the patient as well as to the disease.

TEMPORAL ARTERITIS. This was described by Horton, Magath, and Brown[29]. Usually temporal arteritis may be differentiated from forms of necrotizing vasculitis on the basis of clinical, anatomic, and pathologic findings. Temporal headache, blindness, and hemiplegia commonly result from occlusive vascular ischemia. Fisher[15] has described the ocular manifestations. This arteritis occurs more often in older people and usually is self limiting. Hypertension is often absent. Anatomically the cephalic arteries are affected. Of these the temporal arteries are involved early and in most cases. Rarely the thoracic and abdominal arteries show characteristic changes. Pathologic characteristics include nodular, subintimal inflammation with giant cells and fibrinoid necrosis. Biopsy of the temporal artery may assist in diagnosis.

SCHOENLEIN-HENOCH PURPURA[46]. Gairdner[18] and Lecutier[39] have stated that periarteritis and the Henoch-Schoenlein syndrome are virtually the same disease. It is presumed to be an anaphylactoid vasculitis, resulting from exposure to antigens of food, bacterial infection and therapeutic agents. In this syndrome the smallest arterioles and capillaries mainly are affected. Humble[30] has suggested that the purpura arises primarily in the terminal portion of the arteriole. The manifestations consist of dermal and mucosal purpura, painful melena and hematemesis, hematuria, joint pains, convulsions, and coma. The latter two may be caused by petechial or hemorrhagic cerebral damage. The vasculitis may

begin peripherally with petechiae in the sole and palm and may appear to be most severe in those locations. Hemorrhage and necrosis may be extensive. The lesion is often reversible, infrequently fatal.

PULSELESS DISEASE. Takayasu[51,52,54] and other ophthalmologists first described the prominent arteriolitis of the retina in this disease. It is an inflammatory obstruction of those arterial vessels arising in the aortic arch and perfusing the head and upper extremities. Anatomically and clinically this disease is a cephalobrachial arteritis and arteriolitis. Pulseless disease is so termed because the carotid and brachial pulses are usually absent. It is most common in young women. Causes include luetic arteritis and aortitis, atherosclerosis, trauma, periarteritis nodosa, temporal arteritis, neoplasm, collagen disease and Buerger's disease. Currier, DeJong, and Bole[10] listed the incidence of neurologic signs in an analytic review of 40 cases from the literature. Claudication of mastication and arm activity is common. Temporary loss of vision from retinal ischemia induced by arising from the horizontal to the sitting or standing position is frequent. Syncope may follow postural loss of vision or occur independently. Funduscopic examination often reveals false "microaneurysms," new vessel formation, and optic atrophy. According to Ashton[3] the characteristic arteriolar-venular anastomoses around the optic nerve head may be associated with anoxia. Retinal central vascular thrombosis with atrophy of the iris and aneurysmal changes of the retinal arteriole have been noted by Paterson[47]. Regional ischemia may result in ulcerative necrosis in the nasal septum, face, and ear. If not fatal in 3 years, the development of collateral circulation may favor recovery.

HYPERTENSIVE FIBRINOID ARTERITIS OF THE BRAIN. This pathologic entity was described by Feigin and Prose[14], as a fibrinoid form of hyalinosis probably akin to collagen. It was specifically related to gross cerebral hemorrhage in hypertensive patients. They stated that this arteritis affected only the cerebral arteries ranging from 0.2 mm. to 0.8 mm. in diameter. The fibrinoid arteritis would not be observed in the retina as the arterioles of the latter are less than 0.2 mm. in diameter. Necropsy in patients with this arteritis also demonstrated moderate or severe arteriolosclerosis in the viscera.

GRANULOMATOUS ANGIITIS. Localized periarteritis nodosa must occasionally be differentiated from the following angiitides. These include Wegener's[21, 61] granulomatosis, allergic granulomatous angiitis of Churg and Strauss[7], and noninfectious granulomatous angiitis described by Cravioto and Feigin[9,45]. The granulomatous angiitides respectively affect predominately the respiratory tract, the viscera, and the intracranial arterioles.

HYPERTENSION AND HEMORRHAGE. Multiple small retinal arteriolar hemorrhages may be observed ophthalmoscopically in cases of hypertension, renal vascular hypertension, pheochromocytoma and adrenalin overdosage. The retinal hemorrhage may precede or follow cerebral hemorrhage. Fatal cerebral hemorrhage has been observed in previously nonhypertensive patients with recently developed hypertension in periarteritis nodosa, lupus erythematosus, and pheochromocytoma.

The fundamental facts in hemorrhage in the brain relate to the height and duration of the hypertension and the extent of the disease in the artery or arteriole. The low incidence of classical cerebral hemorrhage in toxic hyperthyroidism suggests that cerebral hemorrhage and its substrata are more closely related to diastolic than systolic

hypertensions. Medial dissolution and aneurysm are the mural lesions most likely to result in hemorrhage. From a clinical point of view hypertension and medial necrosis have many causes.

The arteriolosclerosis and necrosis of hypertension have been related etiologically to periarteritis nodosa by Meyer[44], Klemperer and Otani[34], Child[6], and Wilson and Byron[65]. Contributions to our understanding of arteriolar disease in hypertension have resulted from the observations of Wagener[63], Keith[32], and Kernohan.

PATHOPHYSIOLOGY OF VASCULITIS LESIONS. The classical form of periarteritis nodosa described by Kussmaul and Maier consisted of macroscopic as well as microscopic lesions. In most cases reported in recent years, for reasons unknown, largely microscopic lesions have been demonstrated. The character of the arteriolar lesions in necrotizing vasculitis is of interest.

The nodule is often round. It usually occupies a small arc of the arteriolar wall. Nodular luminal deformation may give rise to intimal damage. This may lead to thrombosis of the arteriole. The nodule of inflammation, fibrinoid necrosis, and thrombosis is segmental. Therefore serial section of a biopsy may be required if the latter is to be diagnostic.

The thickened arteriolar cylinder may be segmental or its length may be several times the vessel diameter. The cylindrical thickening results in impaired distensibility, deformation of the truncated arteriolar cone, atresia, and a pin hole lumen. Altered flow into the capillary is followed by progressive ischemia.

Aneurysm may be single or multiple. Hemorrhage is the natural consequence of aneurysmal rupture. In mural necrosis rupture and hemorrhage may also occur. After rupture, hemorrhage lowers intravascular pressure. Insufficiency of flow then may produce ischemia, infarction, and cellular necrosis.

Bilateral ophthalmoscopic observation and photography of the retinal arteriole, especially when performed periodically, may reveal the following abnormalities in necrotizing vasculitis. In central occlusion the arterioles are reduced to a fine line. The occlusion may affect superior or inferior divisions or quadrant branches with corresponding ischemic attenuation and blindness. Reduction of the retinal arteriole to a fine line distal to the occlusion indicates that the lumen is not perfused.

In periarteritis nodosa, dermatomyositis, lupus erythematosus, and serum sickness, retinal cytoid bodies are often found, especially in moribund patients. In serum sickness, hypersensitivity can not easily be denied. The white elliptical cytoid bodies are often associated with one or two linear striate arteriolar hemorrhages. Cytoid bodies although of unknown pathogenesis are believed to be related to arteriolar dysfunction. This may account for the fact that cytoid bodies are reversible. After remission they may reappear following recrudescence of the underlying vascular lesion.

Functional and organic changes in retinal arterioles are often associated with hypertensive arteriolosclerosis, malignant hypertension, toxemia of pregnancy, and vascular renal disease. Segments of the retinal arterioles may be attenuated. This may be temporary and functional. Edema and "spasm" are believed to be causative. Permanent segmental attenuation of the retinal arteriole suggests a progressive arteriolar lesion. Ophthalmoscopic increased ratio of the diameter of the light streak to that of the arteriole in organic segmental attenuation often indicates irreversible changes in the arteriolar media. Severe sclerosis of the arteriole may produce the ophthalmoscopic ap-

pearance of increased brilliance of the light streak known as the "copper wire" and the "silver wire" deformities. In the "wire" deformities the lumen is narrowed, the wall hardened and thickened, and the arteriolar diameter decreased. Retinal arteriolar changes may reflect similar alterations in cerebral arterioles. Intraocular pressure may protect the retinal arteriole from hypertensive pressures affecting the cerebral arterioles. If this is true cerebral arteriolar changes would exceed those observed opthalmoscopically. The organic changes of the retinal arteriole observed in hypertension are a result of longstanding disease. These changes are therefore often absent in the acute necrotizing vasculitis of collagen disorders.

Older nonhypertensive patients, frequently show a mild increase in width of the ophthalmoscopic light streak and moderate compression of the A-V junctions. The causes of these changes are unknown. The effects of normal blood pressure in producing a physiologic or involutional attrition and fatigue of arterioles have not been evaluated. The sum total of traumata to arterioles during a life time would be expected to produce functional and structural degradation.

The fact that retinal arterioles approximate 0.15 mm. or less in diameter indicates that the major vascular physiologic processes are subserved by arterioles of this size. The large variety of systemic diseases which affect the retinal arteriole signifies the importance of arteriolar patho-physiologic abnormalities.

NEURAL LESIONS IN NECROTIZING VASCULITIS. Periarteritis nodosa and necrotizing vasculitis frequently begin as a febrile neuritis later associated with multiple system abnormality and constitutional responses. The arteriole within the peripheral nerve is often the first site of ischemia. The distal vasa nervorum ischemia in the foot and hand are often productive of the initial symptoms and signs of vasculitis. Paresthesia and burning pain, first in the foot and subsequently in the hand, followed by ascending motor neuropathy and later sensory deficit suggest that certain factors are responsible for the manner of development. These may include the relative sensitivity of nervous tissue to ischemia and anoxia, the length of the neuron, the inadequacy of peripheral collateral circulation, and vasospastic effects. Initially one peripheral nerve may be symptomatic. At the other extreme, all peripheral nerves may become diseased simultaneously. Commonly the vasa nervorum of various peripheral nerves are affected in rapid succession. In cases with Landry's form of ascending motor progression this may be more apparent than real as the vasculitis is disseminate. If the peripheral neuritis advances, its symptoms ascend the extremity, as indeed they must. As the neuropathy ascends, motor weakness assumes an appearance of greater magnitude as impairment of standing, walking, urination, and respiration develop. Once motor weakness has progressed, respiratory functions should be evaluated frequently. Inspection of tidal volume and vital capacity and their measurement with a ventilation meter is advisable. Rapidity of spread and serious illness may mask asymmetry of motor progression. It is believed that vasoneuropathy occurs later in the cranial nerves than in the peripheral nerves. Little is known of visceral denervation syndromes resulting from vasa nervorum ischemia of the cranial and autonomic nerves. The peripheral and cranial vasoneuropathy is a result of progressive luminal attenuation, thrombotic occlusion, and ischemia. In the brain and other viscera

hemorrhage occurs. Glaser[20] has noted the secondary effects occurring in the nervous system as a result of cardiac failure, hypertension, azotemia, and other visceral ischemias.

Conclusions and Summary. Since the Italian Renaissance, respiratory and circulatory anatomy and physiology have grown into complex arts and sciences. Cardiac and pulmonary functions have become phenomena of clinical prominence. This is a result of nervous system preservation being dependent on cardio-pulmonary and arteriolar functions.

Necrotizing diseases of the arteriole are of current interest. Physiologic factors in pathogenesis are important in the prevention and treatment of arteriolitis, and its destructive effects in the nervous system. The arteriole regulates peripheral vascular resistance and therefore sustains blood pressure. The wall of the arteriole contains smooth muscle and collagen and is subject to disease processes affecting these tissues. The tone of arteriolar muscle, hence luminal diameter is subject to neurohumoral controls. These relate to functions of the vasomotor nerves, the carotid sinus, the carotid and aortic bodies, and endogenous substances. Alterations of blood pressure, arteriolar blood flow and capillary supply is an integral part of arteriolitis.

The lesions of necrotizing vasculitis may have a disseminate distribution or may conform to a characteristic pathoanatomic localization. Pathologic entities observed in the arteriole include deformation, inflammation, sclerosis, aneurysm, necrosis, and rupture. These abnormalities result from bacteriotoxins, abnormal immune responses, antigen-antibody effects, chemical sensitizations, metabolic disorders, and unknown reactions. Physiologic correlates include anoxia, ischemia, hemorrhage, shock, and hypertension. These alterations often destroy neural cells. Vascular disease is the ranking killer of man. Destruction of the heart and the brain are responsible for the mortality. In addition the morbidity of cerebrovascular disease invalidates in part the medical triumph of longevity. In evaluation of lesions of the nervous system, the status of the arterioles merits circumspect attention.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF DECEMBER 15, 1959

Anatomical Organization of the Frog and Cat Spinal Cord, Dorsal Root and Propriospinal Pathways. WILLIAM W. CHAMBERS, JAMES M. SPRAGUE AND CHAN-NAO LIU (Department of Anatomy and Institute of Neurological Sciences, University of Pennsylvania). Comparative anatomical studies suggest a progressive evolution of the spinal cord from the chordates to the higher vertebrates (Cajal, 1909; Kappers, Huber and Crosby, 1936). The spinal cord of adult toads and frogs has evolved to the point where it is similar in basic structure to the mammalian spinal cord. The cords are similar in the configuration of the gray and white matter, in the general grouping of cell bodies of the spinal neurons, and in the organization of paired dorsal and ventral roots. However, certain marked differences, can be observed in Golgi, Cajal, Nauta and Rasmussen preparations (Windle, 1958).

The motor neurons of the ventral horn in the frog are large cells elongated dorsoventrally, and the majority of their dendritic processes pass laterally and ventrally in the white matter to ramify extensively just beneath the surface of the lateral and ventral parts of the cord. Axons of the commissural and funicular cells and collaterals from the motor axons also ramify in this peripheral dendritic plexus of the motor neurons to form a perimedullary neuropile. A dorsal neuropile in the posterior white columns just above the dorsal horn is also present in the frog. It is formed by the dendritic processes from some of the dorsal funicular cells and axon collaterals from the dorsal root fibers. The neuropile in the grey matter of the frog is much less dense than in the mammalian cord. The greater synaptic density in the white matter (perimedullary and dorsal neuropiles) can be demonstrated by the Rasmussen stain for synaptic terminals.

Adult frogs (*Rana pipiens*) with section of a dorsal root, cranial nerve, and hemisection of the spinal cord or lower medulla were maintained at a room temperature of 26 to 30° C. and sacrificed from 2 to 53 days postoperatively. The spinal cord and brain were stained by a modified Nauta silver method (Chambers, Liu and Liu, 1956) for the specific staining of degenerating axoplasm. The degenerating axons of the frog show the same general changes and stain similarly to those of the cat (Liu, 1956; Sprague, 1958): 2 days, the fibers are beaded and slightly vacuolated; 7 to 10 days, the fibers are fragmented and the debris is maximum; 20 to 53 days, debris is still present but considerably reduced.

Degenerating axons from all severed dorsal roots in both frog and cat show a medial and lateral division. The lateral divisions of the dorsal root fibers ascend and descend in a dorso-lateral fasciculus for only 1 to 2 segments. The medial division, via ascending fibers in the posterior funiculus, reaches the lower medulla, and via descending fibers may extend for 5 or 6 segments. The ascending fibers of the medial divi-

sion of the dorsal roots are laminated in the posterior funiculus, the most caudal dorsal root occupying the dorsal medial area in the upper spinal segments. The terminal distribution of the dorsal root fibers in the medulla of the frog is in an area just ventral to the descending fibers of the trigeminal nerve, and in the posterior column nuclei of the cat. The dorsal roots terminate in both frog and cat in an orderly lamination in the respective areas, being wholly axodendritic in the frog and axosomatic as well in the cat. The terminal distribution of the medial division of the dorsal root fibers in the spinal cord was limited to the posterior neuropile and dorsal horn for as many as 3 segments rostral and 5 or 6 segments caudal to the entrance of the severed root. No degenerating dorsal root fibers reach the gray matter of the ventral horn, but Golgi preparations indicate the possibility of minimal contact with some motor neuron dendrites which extend into the dorsal horn and may reach the posterior neuropile. The medial dorsal root fibers in the cat terminate extensively in all parts of the spinal gray matter, including the motor nuclei where they form synaptic contacts on both cell bodies and dendrites. The root fibers show division into fascicles which reach specific nuclear areas of the gray matter-motor cells of ventral horn, interneurons of intermediate and dorsal horns, and cells of cerebellar (Clarke) and thalamus (gracile and cuneate) relay nuclei.

The longitudinal pathways of the spinal cord were studied by hemisection at various levels of the cord and lower medulla. Descending degeneration in the frog reached from the medulla to the lowest level of the cord, bilateral in the upper segments, and passed in the lateral white columns. These fibers terminated chiefly in the perimedullary neuropile and on the dendrites in the lateral funiculus, and to lesser extent in the gray matter of dorsal and ventral horns. In the lower spinal segments the degeneration was greatly reduced and entirely ipsilateral. Hemisection at any level of the spinal cord resulted in degeneration on both sides of the cord, heaviest in the segments near the lesion and on the ipsilateral side. Terminal degeneration appeared in the white matter and in the gray matter of the dorsal ventral horns. Degeneration was greatest in the lateral white column and lateral neuropile, less in the posterior white column and dorsal neuropile, and least in the gray matter. However, considerable terminal degeneration was seen around the ventral horn cell bodies and proximal dendrites near the lesion and 2 or 3 segments below the lesion.

In both frog and cat, the short propriospinal fibers form the chief afferent supply of motorneurons, and in the cat terminate in the gray matter on cell bodies and proximal dendrites of the motor cells. In the cat, those descending pathways originating above the medulla terminate in dorsal and intermediate horns, while the medullary-spinal pathways end also in the ventral horn. Thus, as in the case of the dorsal roots, the various descending pathways terminate in specific portions of the gray matter in the cat (see also Szentagothai-Schimert, 1941). The evidence on hand indicates that descending pathways are more sparse in the frog, and suggests that these are less discrete in their pattern of termination in the cord. This evolutionary trend can be seen in the primate in which certain motor neurons are connected directly with the long corticospinal fibers.

The anatomical findings of direct propriospinal connections with the ventral horn cell bodies and proximal dendrites, and the absence of similar con-

nections from dorsal root fibers agree with physiological experiments of Brookhart *et al.*, 1959. They found that the firing of the motor neurons varied markedly with dorsal root and lateral column stimulation. Short latency, highly synchronized discharges which remain stimulus related even at high frequencies occur in ventral horn cells from stimulation of the lateral column but not from the dorsal root. The work of Lloyd (1942) agrees with the anatomical evidence that motor cells are discretely and directly influenced by dorsal roots and propriospinal tracts in the cat.

In summary, the spinal cord of the cat differs from the frog in the 1) increase in number of both cells and fibers and decrease in their relative size, especially the motorneurons, 2) increase in the number of dendrites originating from the cell bodies, and in their greater ramification in the gray matter, 3) better differentiation of cells into nuclei, many with discrete dendritic fields limited to the gray matter, 4) longer axon collaterals extending into the gray matter and divided into separate fascicles to specific nuclei, 5) increase in the synaptic contacts on dendrites and cell bodies in the gray matter, and 6) presence of dorsal root terminals on proximal dendrites and cell bodies of motorneurons.

Experimental Modification of Spinal Pathways Resulting from Transformation of Cellular Processes. Donald Scott, Jr. and Chan-nao Liu. (Departments of Physiology and Anatomy, University of Pennsylvania School of Medicine). Induced collateral branching in peripheral axons has previously been demonstrated in the sensory motor, and sympathetic systems of others. It has also been possible to demonstrate increased arborization of the intraspinal terminals of dorsal root fibers as a result of section and degeneration of neighboring fiber bundles.

Since the dorsal spinocerebellar tract is completely intraspinal, alterations in its distribution were studied by the evoked potential method subsequent to a unilateral lesion in the cervical or thoracic region. Stimulation of a lumbar dorsal root contralateral to the lesion not only evoked a characteristic response on the unoperated side but it was also possible to record a potential response on the operated side above the level of the lesion. Since this ipsilateral response to contralateral dorsal root stimulation was not abolished by a subsequent cord transection 5 cm. above the level of the original lesion, no cerebellar relays appear to be involved. The hypothesis that this potential is conducted by commissural branches from the normal fibers of the dorsal spinocerebellar tract on the unoperated side receives strong support from the observation that it can be abolished by an appropriate midline longitudinal section.

Evidence for such branching collaterals has been obtained following a postoperative period between 128 and 531 days, during which no therapy was administered. Evoked potentials of this type have been recorded over 30 mm. above the level of the lesion. The same type of response was obtained when stimulation was applied directly to the dorsal spinocerebellar tract on the unoperated side below the level of the lesion. Stimulation of either the dorsal spinocerebellar tract or the lumbar dorsal root below the level of the lesion on the operated side failed to evoke any potential above the level of the lesion.

The Intracellular Approach to Synaptic Conduction in the Spinal Cord. Karl Frank, Ph.D. (National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland). Information from the sensory receptors reaches the central nervous system over the peripheral

nerve fibers by a system of pulse frequency modulation. These trains of coded messages produce reactions in other nerve cells by at least three basic mechanisms. (1) Impulses in excitatory afferent terminals are thought to release a chemical transmitter substance which produces a selective permeability change in the postsynaptic membrane for certain ions resulting in depolarization of the postsynaptic cell. If a trigger area, the A area, is depolarized to its threshold level, the cell discharges. (2) Direct inhibition acts by hyperpolarizing the cell membrane so that any given excitatory volley finds it more difficult to bring the trigger area to threshold. Inhibitory hyperpolarization is thought to be the result of a conductance change to different ions produced by presynaptic release of an inhibitory transmitter substance. The direct inhibitory pathway involves a longer transmission time than does excitation, possibly implying a disynaptic inhibitory pathway. (3) Remote inhibition reduces the effectiveness of a test excitatory volley without, by itself alone, producing any measurable potential change in the postsynaptic cell membrane. Excitability of the cell membrane is also unchanged as measured by threshold depolarizing pulses delivered through an intracellular micropipette electrode. Shocks to the ipsilateral hamstring nerve remotely inhibit a test gastrocnemius reflex if they precede it from 7 to 80 msec. It is suggested that interaction between presynaptic fibers tends to block conduction, or release of transmitter, by the smaller, slower conducting excitatory afferent fiber branches.

BOOK REVIEWS AND NOTICES

HANDBOOK OF TOXICOLOGY. VOLUME IV: TRANQUILIZERS. Edited by RUDOLPH M. GREBE. Prepared under the direction of the Committee on The Handbook of Biological Data, Division of Biology and Agriculture, The National Academy of Sciences, The National Research Council. Pp. 120. Philadelphia: W. B. Saunders Company, 1959. Price, $4.00.

THE fourth volume of the Handbook of Toxicology deals with the toxicology of tranquilizers. Included are the so-called tranquilizers of reputed value which are presently available, and among them the so-called psychic energizers. Considering the widespread use of this group of drugs, with the inevitable occurrence of abuses, this volume on the toxicology of these agents is welcome and timely. Physicians using these drugs and anyone concerned with toxicologic problems should find this a valuable reference. The book is arranged in 26 sections, each dealing with one drug and each followed by references. The index lists all names of drugs and alternative names, alphabetically, and thus serves as a cross index. R.S.

HANDBOOK OF TOXICOLOGY. VOLUME V: FUNGICIDES. Edited by DOROTHY S. DITTMER. Prepared under the direction of the Committee on The Handbook of Biological Data, Division of Biology and Agriculture, The National Academy of Sciences, The National Research Council. Pp. 241. Philadelphia: W. B. Saunders Company, 1959. Price, $5.50.

THE fifth volume of the Handbook of Toxicology deals with the toxicity of fungicides and includes all fungicidal agents for which toxicity data were available. The book is arranged alphabetically in 196 sections, each dealing with a particular agent. An appendix lists 500 additional compounds. References are grouped together at the end of the text. For easy reference, the index includes all the more common alternative names for each compound.

R.S.

COLD INJURY. TRANSACTIONS OF THE FIFTH CONFERENCE. Edited by M. IRENÉ FERRER, M.D. Pp. 341; 73 ills. New York: Josiah Macy, Jr. Foundation, 1958. Price, $5.95.

THIS volume, like its predecessors, is a stenographic report of informal round table discussions among a group of experts in various fields of cold injury.

The topics discussed include animal adaptation to cold, hibernation, ventricular fibrillation in acute hypothermia, use of glycine in hypothermia, human acclimatization to cold, energy metabolism in cold and avenues of heat loss and peripheral circulation.

The interchanges among the participants are lively and critical with no holds barred. Much of the material presented may appear to have little direct clinical application. However, the fact that hypothermia has recently been found useful in neurosurgery and hemorrhagic shock as well as in open heart surgery makes this data important for the practicing physician as well as the investigator.

N.L.

SYPNOPSIS OF OPHTHALMOLOGY. By WILLIAM H. HAVENER, M.D., Professor and Chairman, Department of Ophthalmology, Ohio State University. Pp. 282; 189 ills. St. Louis: C. V. Mosby Co., 1959. Price, $6.75.

THIS small book is carefully planned to give a maximum of information in a form that can be used by persons who are not specialists in ophthalmology.

The more common eye difficulties are discussed briefly and well illustrated. This book is a very valuable aid to diagnosis and is beautifully supplemented by a section on therapy. The treatment is presented in a way that enables the person following this outline to use the proper medication in the proper way for the most common conditions.

I am very enthusiastic about this book. It will be a valuable reference text for any receiving ward. L.H.

THE CARE OF MINOR HAND INJURIES. By ADRIAN E. FLATT, M.A., M.D., F.R.C.S., Assistant Professor of Orthopedic Surgery, State University of Iowa, Iowa City, Iowa. Pp. 257; 109 ills. St. Louis: The C. V. Mosby Company, 1959. Price, $9.50.

THE author, in his introduction, states that this book has been written in a fashion that enables an individual to go to a section and read it without the need of referral to other sections to find pertinent and needed informa-

tion. This is offered as an explanation for the repetition which is found in the book. I think the author has done what he has tried to do; that is, to make this somewhat of a reference book for the care of minor injuries to the hand that he defines as injuries that can be treated on an outpatient basis. The book is well illustrated, is prefaced by a lucid section on functional anatomy of the hand and I think offers sound principles of therapy. R.T.

SECOND CONFERENCE ON PHYSICOCHEMICAL MECHANISM OF NERVE ACTIVITY AND SECOND CONFERENCE ON MUSCULAR CONTRACTION. BY DAVID A. NACHMANSOHN AND ALEXANDER SANDOW AND 27 OTHERS. (Ann. New York Acad. Sci., Vol. 81, Art. 2). Pp. 295; illustrated. New York: New York Academy of Sciences, 1959. Price, $4.00.

THE rapid advances in our understanding of the mechanisms underlying nerve activity and muscular contraction are reflected in this symposium. The first part is highlighted by A. F. Huxley's discussion of ion movements during nerve activity and Eccles' survey of excitatory and inhibitory synaptic action. The second part deals with the basic organization of fibrils as revealed by electron microscopy, with the coupling of the electric events of the membrane to activation of the mechanical response of the contractile system and the mechanochemistry of the living muscle. In view of the multitude of data presented, summarizing statements would have greatly added to the value of this monograph E.S.

METABOLIC CARE OF THE SURGICAL PATIENT. BY F. D. MOORE, M.D., Moseley Professor of Surgery, Harvard Medical School. Pp. 1009; 143 ills. Philadelphia: W. B. Saunders Company, 1959. Price, $20.00.

THE present-day surgeon requires knowledge and skills far beyond those of diagnosis and the dextrous use of instruments. There has developed during the past 20 years, with much impetus gained during World War II, a considerable mass of data dealing with stress reactions; the surgeon who deals with these responses daily has to understand metabolic realities. In this important area of surgical care, the author has been a devoted student and teacher who has succeeded in amalgamating the basic patterns of metabolism, endocrinology and convalescence with the problems of clinical management in surgery.

Simplification of the complex array of material is achieved by dividing the book into six main sections each with its own index, discussions, and case summaries illustrating every conceivable aspect of the metabolic management in surgery. The sections deal with body composition, blood volume, fluids and electrolytes, nutritional aspects, visceral diseases, and traumatic injuries providing a wealth of information obtained from a wide experience with many newer techniques of investigation and an enormous bibliography on these subjects. The careful study of this important authoritative volume should be required of all physicians involved in the care of surgical patients. C.S.

PRINCIPLES OF DISABILITY EVALUATION. BY WILMER CAUTHORN SMITH, M.D., Chief Medical Advisor, Oregon State Industrial Accident Commission. Pp. 204; 2 ills; 1 in color. Philadelphia: J. B. Lippincott Company, and London: Pitman Medical Publishing Co. Ltd., 1959. Price, $7.00.

THIS is an excellent and much needed text on disability and its evaluation. Out of his extensive experience in the field, the author has derived a number of useful and valid general principles that have wide application in all areas of disability. It is a text that is recommended for all physicians who meet this problem, and who does not these days? It contains the best section on medical testimony this reviewer has seen. W.S.

PROCEEDINGS OF THE WORLD CONGRESS OF GASTROENTEROLOGY AND THE FIFTY-NINTH ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION, 2 vols. Pp. 1363; illustrated. Baltimore: The Williams & Wilkins Co., 1959. Price, $20.00.

ALMOST two thousand gastroenterologists representing over 50 countries met in Washington in May, 1958, to attend the World Congress and the meeting of the A. G. A. The published proceedings of these meetings include original contributions, symposia, panel discussions and special presentations such as the Pavlov lecture delivered by K. M. Bykov (deceased) of Russia. Although peptic ulcer, cancer and the like were accorded their proper respect, diseases of the small intestine received the greatest attention. Three symposia, three sessions of original contributions and many panel discussions were devoted to affections, infections, infestations and tumors

of the small intestine. The symposium on malabsorption, which was particularly outstanding, included contributions by Wollaeger, Weijers, van de Komer, Hernández-Morales, Shiner, Cooke and Adlersberg as well as others. Jan Waldenstrom's discussion of the clinical picture of carcinoidosis was also commendable.

A list of authors who made contributions to these volumes would read like a "who's who" in world gastroenterology. Those interested in global medicine will be particularly intrigued by the opportunity to review epidemiologic and clinical features of a variety of disorders and diseases that affect the gastrointestinal tract. The chairman of the congress, H. L. Bockus, and his associates deserve congratulations for publishing these proceedings which could well serve as a textbook of modern gastroenterology. S.L.

Clinical Scalar Electrocardiography. By Bernard S. Lipman, A.B., M.D., F.A.C.P., Associate in Medicine, Emory University School of Medicine, and Edward Massie, A.B., M.D., F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine. 4th ed. Pp. 474; 339 ills. Chicago: The Year Book Publishers, Inc., 1959. Price, $8.00.

The fourth edition of this book is a tribute to its popularity and success or perhaps to the popularity of electrocardiography. The authors attribute its success to its simplified manner of presentation, an admirable quality suitable for the beginner.

This edition is 70 pages longer than the third. This enlargement is due to inclusion of short discussions of electrocardiographic theories and a chapter on orthogonal lead systems which is too superficial to be meaningful. Peri-infarction and focal block have been added. Anomalous atrial ventricular conduction has been changed to Wilson's term anomalous atrioventricular excitation.

In general, this book represents a simplified version of Wilson's concepts and in this sense it may be recommended for beginners. Perhaps the best part of the book for the non-specialist is the large number of illustrations. L.S.

A Textbook of General Physiology. By Hugh Davson, D.Sc.(Lond.), University College, London. 2nd ed. Pp. 820; 384 ills. Boston: Little, Brown and Co., 1959. Price, $14.50.

In this second and larger edition the excellent qualities of the first have been retained. Several new chapters on sensory response, excitability of heart and on electrical activity of involuntary muscle have been added. All of the older presentations have been expanded and brought up-to-date. The chapters on equilibria, on permeability and the plasma membrane, and the one on ionic equilibria, bioelectric potentials and active transport seem especially outstanding.

M.O.

Master Your Tensions and Enjoy Living Again. By George S. Stevenson, M.D., National and International Consultant, National Association for Mental Health; and Harry Milt, Public Relations Director, National Association for Mental Health. Pp. 241. New York: Prentice-Hall, Inc., 1959. Price, $4.95.

The authors attempt to convey to the reader that distortion in human reactions can be controlled by the simple, albeit difficult, expedient of volitionally following a certain set of rules. This aim, however, seems inconsistent with the following paragraph quoted from Chapter 6:

> "It would be wonderful if you could, on our suggestion, or anyone's suggestion, decide to change your personality and overnight become an easy-going, outgoing, confident person with a high opinion of yourself. But personality traits aren't changed that easily. They've developed over the many years that you have lived and are, by this time, pretty well established."

To its credit, the book has a style which makes for easy reading. Chapters on tension, anxiety and child behavior are realistically educational.

This book may meet the prevailing anxious need on the part of many to have black and white rules to live by. These people, however, usually need more than rules that the authors hope will be gleaned from their work to achieve the comfort in everyday living.

K.C.

Diagnosis and Treatment of Menstrual Disorders and Sterility. By S. Leon Israel, M.D., Professor of Obstetrics and Gynecology, Graduate School of Medicine, University of Pennsylvania. 4th ed. Pp. 666; 146 ills. New York: Paul B. Hoeber, Inc., 1959. Price, $15.00.

Israel, who is now the sole active author

of "Menstrual Disorders and Sterility," has proven beyond question that a textbook of endocrinology can be interesting, practical and helpful in solving clinical problems while it still contains a considerable amount of information concerning the basic laboratory research from which methods of treatment have been developed. As he states in the preface the book is ". . . intended as a guide for all physicians interested in the diagnosis and treatment of menstrual disorders and sterility. Contributions from workers in the fundamental sciences have been examined with the objective of translating their more pertinent findings into words of practical usefulness. . . ." Although he has practically rewritten the entire book the arrangement of the material is much the same as in previous editions. Excellent discussions of the male factors in infertility by Charles W. Carney and of the thyroid and adrenal glands in menstrual disorders by Norman G. Schneeberg are included.

The physiologic activities of the various endocrine organs which control genital function are discussed in detail as are growth and development in the female. Considerable space is devoted to discussions of the various bleeding abnormalities but other problems related to menstruation are also considered; for instance premenstrual tension, dysmenorrhea, migraine, breast hyperplasia and Mittelschmerz. The section on infertility is especially good.

Since the author is a practicing obstetrician-gynecologist and not a pure laboratory endocrinologist it is not surprising that he is aware of the emotional problems which are so often present in women with gynecologic disorders. It is surprising, however, and realistic that this aspect is presented with such understanding. It appears that the author is anticipating and preparing for a rapid expansion of knowledge concerning the interplay between emotions and dysfunctions of endocrine glands. He hopes cautiously that ". . . the reader will sense the necessity of a closely knit relationship between hormonal treatment and an encouragingly supportive attitude of the physician toward the patient and her surrounding life forces." The frontispiece is a display of the relation of the hypothalamus to the pituitary gland.

A major alteration in therapeutic philosophy concerns low dosage gonadal irradiation in certain menstrual disorders. Mazer and Israel, who have long been proponents of ovarian radiation and who have reported excellent results, have recently given it up because of their concern over its effect on germ plasm.

The text is well illustrated with photographs, photomicrographs and tables and the efficacy of the recommended methods for studying and treating the various conditions are well documented by results from the author's vast experience. The bibliography is detailed.

This excellent book should prove helpful to specialists, family physicians, residents and medical students. In short it is one of the outstanding available volumes on genital function in women. J.W.

A Manual of Anaesthetic Techniques. By William J. Pryor, M.B., Ch.B., (N.Z.), F.F.A.R.C.S. (Eng.), D.A. (Eng.), F.F.A.R.A C.S., Anaesthetist. Thoraic Unit, Christchurch Hospital, (N.Z.) and Late Anaesthetic Registrar, The London and Popular Hospitals, London. 2nd ed. Pp. 238; 75 ills. Bristol, England: John Wright & Sons, Ltd., 1959 (The Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $7.00.

This is an extremely well written manual and seems to have been written especially for interns and residents. The author has compiled a brief but complete treatise of the present-day anesthetic drugs and techniques.

It is a pleasure to find a book which is so practical as this is. The author, in a very concise manner, describes a well equipped induction room, equipment and instruments normally available, and the agents and materials usually employed in producing general and regional anesthesia.

Three chapters of special value are: Emergency Anaesthesia and Resuscitation, Anaesthetic Emergencies and Difficulties, Post-Operative Care, Complications and Treatment.

The chapter on spinal anesthesia is not complete. The author gives his reasons for the weakness of this section.

This book should be of value to all physicians participating in the administration of anesthetics. L.K.

Dermatologie und Venereologie, Band III. Teil II. Edited by H. A. Gottron und W. Schönfeld. Pp. 705. 317 ills. some in color. Stuttgart: Georg Thieme Verlag, 1959 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $42.40.

Volume III part 2 of this projected work in five volumes, continues the high quality exhibited by the previously issued parts of this series (Am. J. Med. Sci. 237, 543 and 674, 1959). This particular section contains

information written by qualified authorities on diseases of the cutaneous appendages, including acne and rosacea, and an excellent discussion of: The disturbances of function and diseases of the sweat glands; sebaceous gland disorders (acne vulgaris); diseases of the hair and nails; discussion of the cutaneous changes in diseases of the gastrointestinal tract; deficiency diseases and avitaminoses, especially pellagra; skin and liver and pancreas. Relationship between diseases of the skin and the urinary organs; changes of the skin in pregnancy; skin and mineral metabolism; skin diseases of storage of autogenous substances; endocrinologically-conditioned cutaneous changes; leukemia of the skin; lymphogranulomatosis of the skin; mycosis fungoides; cutaneous diseases in internal disturbance; pruritus and trophangioneuroses of the skin. There is, in addition to the unusually complete text, an excellent bibliography at the end of each section. This particular volume contains the author and subject index of both parts of volume III. The high caliber of this work, manifested in all volumes issued to date, promises it an important place in the libraries of dermatologists as well as those of practitioners of many other disciplines of medicine. H.B.

SMOKING, LUNG CANCER AND YOU. By ROBERT N. C. MCCURDY, M.B., CH.B., D.P.H. Medical Office of Health to: Swaffham Rural District Council, Swaffham Urban District Council, Thetford Municipal Borough, and Wayland Rural District Council. Pp. 72. New York: Robert M. McBride Company, 1959.

DR. MCCURDY has apparently addressed this book to the general public, as well as the medical profession, in an effort to get a more widespread acceptance of the evidence which is presently at hand which suggests that lung cancer is caused by smoking. He evidently feels that some powerful forces have been at work to try to suppress the facts and he presents his thinking in this regard in a rather argumentative fashion. The book does serve the purpose, however, of getting a good bit of the data published elsewhere summarized in one form without becoming involved in a mass of figures. It is difficult to review the data which are available without agreeing that prolonged heavy cigarette smoking has a profound effect upon the incidence of cancer of the lung. Dr. McCurdy's point is probably well taken that these data should be presented honestly to the public. Whether this information would greatly influence the habits of the present and future generations is still open to some question. J.J.

SYNOPSIS OF GYNECOLOGY. By ROBERT JAMES CROSSEN, M.D., DANIEL WINSTON BEACHAM, M.D., AND WOODARD DAVIS BEACHAM, M.D. 5th ed. Pp. 340; 106 ills. St. Louis: C. V. Mosby Co., 1959. Price, $6.50.

PREVIOUS editions of *Synopsis of Gynecology* have actually been Synopsis of Crossen's well known text "Diseases of Women" but with the addition of two new collaborators the material has been extensively rearranged and revised. Basic physiologic and anatomic principles, as well as modern and generally accepted methods for diagnosis and treatment are presented clearly and succinctly; descriptions of operative technique are omitted. Methods of management are clearly and definitely presented and psychosomatic aspects of gynecologic care are presented in appropriate places. The addition of a bibliography at the end of each chapter adds greatly to the value of the book.

This volume should be particularly helpful to family physicians and students for quick reference and review, but it is not detailed enough for specialists and residents. J.W.

BEITRAEGE ZUR MANUELLEN THERAPIE. By J. C. TERRIER. Pp. 173; 25 ills. Stuttgart: Hippokrates-Verlag, 1959. Price, DM 24.50.

THE International Congress of Manual Therapy held in Baden, Switzerland, united many prominent West-European physicians interested in the theory and practice of manipulation of spinal and other joints. Incorporation of this form of therapy into classical medicine and establishment of reliable indications and contraindications signifies a long overdue departure from the traditional monoply of outsiders. The presented papers were carefully edited and published in their original languages: English, French and German. The pathological, roentgenological and clinical observations and therapeutic techniques give a well rounded picture of manipulation of spinal joints. Trilingual summaries of each article permit a fast orientation.

This book contains a great deal of stimulating information of practical significance to orthopedists and physiatrists. I.K.

TROPHOBLAST AND ITS TUMORS (Ann. New York Acad. Sci., Vol. 80, Art. 1). By

WILLIAM B. OBER AND 40 OTHERS. Edited By OTTO V. WHITLOCK. Pp. 284; 17 ills. New York: New York Academy of Sciences, 1959. Price, $3.50.

THIS book contains the papers and discussions presented during a symposium sponsored by the New York Academy of Sciences. The participants include basic scientists and clinicians well known for their studies of normal and abnormal placental growth. In the first section (Fundamental Concepts) basic trophoblastic functions of invasion and hormone production are considered. The genesis, growth, patterns, diagnosis and treatment of hydatidiform mole and choriocarcinoma are discussed in the last two sections.

Clinicians as well as pathologists and endocrinologists can learn much from a study of this report. The material is well illustrated and documented with case reports and analyses of clinical end results and extensive bibliographies are included. J.W.

THE VIRUSES: BIOCHEMICAL, BIOLOGICAL, AND BIOPHYSICAL PROPERTIES. VOL. I: GENERAL VIROLOGY; VOL. II: PLANT AND BACTERIAL VIRUSES; VOL. III: ANIMAL VIRUSES. Edited by F. M. BURNET AND W. M. STANLEY. Pp. 609, 408 and 428 respectively; illustrated. New York: Academic Press, Inc., 1959. Price, $16.00, $13.00 and $12.00 respectively.

THESE three volumes represent the most comprehensive survey yet available on the nature and multiplication of viruses. Volume I, devoted to a survey of viruses, includes an introductory statement of the "Problems of Virology" by Drs. Burnet and Stanley. The total of twelve chapters includes "Physical Properties of Infective Particles" by Howard K. Schachman and Robley C. Williams, "Structural and Chemical Architecture of Host Cells with special reference to the synthesis of polymers" by Seymour S. Cohen, "Quantitative Relationships Between Virus Particles and Their Functional Activity" by Carlton E. Schwerdt, "Inactivation of Viruses" by S. Gard and O. Maaloe, "The Chemical Basis of the Infectivity of Tobacco Mosaic Virus and Other Plant Viruses" by H. Fraenkel-Conrat, "The Comparative Chemistry of Infective Virus Particles and Their Functional Activity" by E. A. Evans, "The Comparative Chemistry of Infective Virus Particles and of other Virus-specific Products: Animal Viruses" by Werner Schafer, "Biochemistry of Insect Viruses" by G. H. Bergold, "The Scope and Limitations of Immunological Methods in the Characterization and Functional Study of Viruses" by F. M. Burnet, and "The Reproduction of Viruses: a comparative survey" by S. E. Luria.

Volume II contains chapters on "The Process of Infection and Virus Synthesis with Tobacco Mosaic Virus and Other Plant Viruses" by Samuel G. Wildman, "The Biochemistry of Plant Viruses" by Roy Markham, "Variation and its Chemical Correlates" by C. A. Knight, "Biological Cycles of Plant Viruses in Insect Vectors" by L. M. Black, "Bacteriophage as a Model of Host-Virus Relationship" by Andre Lwoff, "The Initiation of Bacteriophage Infection" by Alan Garen and Lloyd M. Kozloff, "Intracellular Multiplication of Bacterial Viruses" by Gunther S. Stent, "Bacteriophage Genetics" by Cyrus Levinthal, "Lysogeny" by François Jacob and Elie L. Wollman, and "Radiobiology of Bacteriophage" by Franklin W. Stahl.

Volume III contains "Animal Viruses; a comparative survey" by F. M. Burnet, "The Initiation of Infection by Animal Viruses" by F. M. Burnet, "Hemagglutination by Animal Viruses" by S. G. Anderson, "Chemistry of Virus Receptors" by Alfred Gottschalk, "The Morphological Approach" by F. B. Bang, "Biological Aspects of Intracellular Stages of Virus Growth," by Alick Isaacs, "Interference between Animal Viruses" by R. Walter Schlesinger, "Inhibition of Multiplication" by Frank L. Horsfall, Jr., "Variation in Virulence in Relation to Adaptation to New Hosts" by Frank Fenner and John Cairns, "Serological Variation" by T. Francis, Jr., "Genetic Interactions Between Animal Viruses" by F. M. Burnet, "Problems Concerning the Tumor Viruses" by Howard B. Andervont, and "The Insect Viruses" by Kenneth M. Smith.

Each of these chapters is written by a distinguished authority in his field and is encyclopedic in scope and will remain the definitive source of reference material until a new edition is published.

The orientation is toward the laboratory virologist rather than any particular concern with the immediate clinical problems in medical virology. M.K.

ALLGEMEINE PATHOLOGIE. BY PROF. DR. E. LETTERER, University of Tübingen. Pp. 850; 632 ills. Stuttgart: Georg Thieme Verlag, 1959 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $16.45.

THIS impressive textbook by the father of Letterer-Siwe's disease presents a broad discussion by a mature teacher of metabolic and

circulatory disturbances of cells and tissues, of tumors and other growth disturbances, and of inflammation. It is essentially a descriptive text, the emphasis being on morphology. Also, it is a philological text with emphasis on definitions and conceptions. Hence, it is an excellent exercise in concise medical thinking. The American reader will admire the more than 600 beautiful illustrations contained in the book, but he will miss some of the scientific clarity to which he is accustomed. There is a lack of biochemical and functional data. There is reluctance by the author to consider the results of experimental pathology. Also, the quoted references are often second hand due perhaps to lack of modern library facilities in the small University in which he works. With these limitations in mind, however, the book is warmly recommended especially to professional pathologists who wish to improve their teaching. W.E.

THE LIFE AND TIMES OF SIR CHARLES HASTINGS: FOUNDER OF THE BRITISH MEDICAL ASSOCIATION. BY WILLIAM H. MCMENEMEY, M.A., D.M., F.R.C.P., D.P.M. Pp. 516; 73 ills. on 32 plates. Edinburgh and London: E. & S. Livingstone, Ltd., 1959 (The Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $10.00.

THIS book is well named. In visualizing the "times" much more space, for instance, is given to the activities of the British Medical Association and its predecessor, the Provincial Medical and Surgical Association, both of which Hastings founded in 1858 and 1832, than to the life of their founder. Appreciation of his ability, to be sure, is manifest, often indirectly, in the accounts of his societies' and hospital meetings, of the much agitated steps in medical reform, hydropathy and homeopathy, of Thomas Wakley and the Lancet, the General Medical Council, and similar matters. Frequent are the references to Hastings' skill in influencing medical opinion, his frankness in acknowledging an error, and the esteem in which he was held by the medical profession generally. In his private work, he was an early user of the stethoscope, and kept careful clinical and necropsy notes of his cases, not a few of which were published. He spoke, and published, on the bad effects of tobacco, the cause of diabetes mellitus, which he ascribed to "organs subservient to alimentation," and in one necropsy report spoke of the inflamed state of the pancreas. His association of childhood inflammation of the mesenteric lymph nodes with hydrocephalus suggested the gastrointestinal origin of tuberculous meningitis. In his attempts to further medical progress, in addition to postmortem examinations, he occasionally carried out experiments on animals to test this or that hypothesis.

An example of the breadth of his interests is to be seen in his work on "Illustrations of the Natural History of Worchestershire," published in 1834. He was knighted in 1850, and not long after a Hastings medal was created by the Association, to be given annually. He was interested in the reform of lunacy laws, and acted as president of the Association of Medical Officers of Asylums for the Insane.

Finally, the excellent illustrations, most of the 73 being portraits, in themselves give a good picture of the Hastings' period. Dignified, elderly, most of them wearing beards or side whiskers, these doctors convey an impression of devotion to their profession and a reliability that produced solicitude for their patients and as good treatment as the paucity of the medical knowledge of the day would permit. In all this Sir Charles Hastings played a prominent role. E.K.

A GUIDE TO THE IDENTIFICATION OF THE GENERA OF BACTERIA. BY V. B. D. SKERMAN, University of Queensland, Australia. Pp. 217; 31 ills. Baltimore: The Williams & Wilkins Co., 1959. Price, $5.50.

WHEN bacteriologists need to identify a bacterial culture they often consult Bergey's *Manual*, the unabridged dictionary of microbial species. The *Manual*, however, is a comprehensive reference volume and not a teaching tool. In order to make it so Skerman has produced a small book which could appropriately be titled "A Practical Guide to Bergey's *Manual*." Although the author states that his guide is intended as a supplement to the *Manual*, he must expect them to be used the other way around since his introductory 48-page Key to Genera refers the reader to specific pages in the *Manual*.

He calls the main section Digest of Genera and achieves brevity by including only one prototype species for each genus. The excellent 60-page section on methods contains the most important techniques and media formulae that are required for the differentiation of bacterial genera. This reviewer was surprised and pleased to find there the formula for Levinthal Hemophilus medium in its several forms. Completing the book is a 4-page Guide to Study which groups together genera of the same general nature for

the benefit of the student of taxonomy. It is also useful for classifying unidentified bacteria. The index seems to be complete.

The author is to be congratulated upon the great care with which this guide was assembled, and the publisher deserves praise for making this an inexpensive paperback book. E.S.

The Evolution of Man's Capacity for Culture. Arranged by J. N. SPUHLER, University of Michigan. Pp. 85; 8 ills. Detroit: Wayne State University Press, 1959. Price, $3.50.

THIS collection of six essays studies the effect of culture on man's biological evolution. It shows how cultural forces replaced environmental factors as the main selective gradient determining the development of man's body and mind. Various phases of biological and social development are traced. A paper by S. L. Washburn shows how the introduction of tools created new selective pressures which led to changes in the hand, face, and brain. J. N. Spuhler analyzes the biological prerequisites to culture such as cortical control of sexual behavior, an expanded cerebral cortex, diet, and bipedal locomotion. R. W. Gerard summarized current thinking concerning the evolution of the nervous system and raises thoughtful questions regarding the effect of physiological differences of the nervous system upon behavior. To those working in the fields of psychology and psychiatry, M. Sahlin's essay, "The Social Life of Monkeys, Apes, and Man," would seem to be of particular interest since it traces back to early primate society, the substitution of culture for instinct as the direct determinant of social behavior.

This symposium is a brief reminder that a study of man's past is an immense aid to an understanding of his current behavior. It is also worthy of note that man's psychosexual development from infancy to adulthood in many ways recapitulates the evolutionary patterns described above. L.S.

Current Trends in Research and Clinical Management of Diabetes. (Ann. New York Acad. Sci., Vol. 82, Art. 2). BY PETER H. FORSHAM AND 93 OTHERS. Pp. 448; 332 ills. New York: New York Academy of Sciences, 1959. Price, $4.50.

THE increasing need for communication of rapidly expanding knowledge concerning diabetes is exemplified admirably in this symposium. The extensive list of collaborators and the inevitable wealth of new data presented make the study of this volume mandatory for those interested in the disease from any aspect, whether socioeconomic, genetic, pathological, physiological or therapeutic. C.S.

Atlas of Human Anatomy. BY SAMUEL SMITH. Edited by M. F. ASHLEY MONTAGU. Anatomic charts by FRANZ FROHSE AND MAX BRÖDEL. Illustrations of Endocrine System by LEON SCHLOSSBERG with text by C. F. GESCHICKTER. 5th ed. Pp. 180; 104 ills., including 49 in color. New York: Barnes and Noble, Inc., 1959. Price, $2.95 (paper); $4.50 (cloth).

THE only commendable features of this low-priced paperbound book are the beautiful color reproductions in miniature of the accurately designed wall charts of Frohse-Brodel. The over simplified explanatory text is really more biologic than anatomic. The purely anatomic part is loosely written (autonomic nervous system, trachea, fetal circulation), incomplete (mammary gland, urinary bladder, liver, lung, blood cells) and often misleading (abdominal wall and inguinal hernia, glottis).

A larger booklet with a full page of purely anatomic description for each of the famous Frohse charts would be a more valuable aid in anatomic instruction than the Atlas is in its present form. N.M.

A Primer on Common Functional Disorders, BY JACK W. FLEMING, M.D., Department of Internal Medicine, The Medical Center Clinic, Pensacola, Florida. Pp. 174; 13 ills. Boston: Little, Brown and Company; London: J. A. Churchill, Ltd., 1958. Price, $5.00.

THIS "primer" is so elementary that it is difficult for the reviewer to imagine that any modern physician would need it. It contains nothing new. Almost the only therapy offered for psychophysiologic reactions is rational explanation of the physiological mechanisms involved. It would be nice if this were as effective as the author would have the reader believe. It just isn't. W.S.

Amine Oxidase Inhibitors. (Ann. New York Acad. Sci., Vol. 80, Art. 3, pp. 551-1045). BY D. WAYNE WOOLLEY AND 97 OTHERS. Pp. 494; illustrated. New York Academy of Sciences, 1959. Price, $5.00.

My Fight for Sanity. BY JUDITH KRUGER. Pp. 244. Philadelphia: Chilton Company, 1959. Price, $4.95.

MRS. KRUGER presents an absorbing and vivid description of a young woman's experiences during her psychotic depression following childbirth. Her spontaneous and fluid style is refreshing and well-adapted to the material conveyed, and succeeds in portraying her intimate feelings and sensitivities in the midst of a profound psychiatric illness.

The book is concerned with two major aspects of her illness: her hospitalization and her intensive psychotherapeutic sessions. In the first part she graphically perceives the unique world of the mental hospital with its uncertainties, fears, and strange meshing of doctors, nurses, and patients. However, the description of her daily routine becomes somewhat tiresome toward the end of her confinement. She surmounts the acute phase of her illness. The terrifying experience of returning home and assuming the role of the loving wife and

mother is only to be achieved through the painful process of what appears to be a face to face analysis. The latter part of the book is exceptionally dynamic and gains in momentum with the increasing force of her revelations. C.K.

Psychophysiological Reactions to Novel Stimuli: Measurement, Adaptation, and Relationship of Psychological and Physiological Variables in the Normal Human. (Ann. New York Acad. Sci., Vol. 79, Art. 3, pp. 43-107). By Roscoe A. Dykman, William G. Reese, Charles R. Galbrecht and Peggy J. Thomasson. Pp. 64; illustrated. New York: New York Academy of Sciences, 1959. Price, $2.50.

Recent Contributions to Antibacterial Therapy (Ann. New York Acad. Sci., Vol. 82, Art. 1, pp. 1-190). By Paul S. Rhoads and 54 others. Pp. 190; illustrated. New York: New York Academy of Sciences, 1959. Price, $2.50.

Enzymes of Polynucleotide Metabolism. (Ann. New York Acad. Sci., Vol. 81, Art. 3, pp. 511-804). By Jay S. Roth and 51 others. Pp. 293; illustrated. New York: New York Academy of Sciences, 1959. Price, $5.00.

Hypothermia. (Ann. New York Acad. Sci., Vol. 80, Art. 2, pp. 285-350). By A. Cecil Taylor and 31 others. Pp. 65; illustrated. New York: New York Academy of Sciences, 1959. Price, $3.50.

Care of the Patient with a Stroke. By Genevieve Waples Smith, R.N., M.A., University of Oregon Medical School. Pp. 148; 66 ills. New York: Springer Publishing Co., Inc., 1959. Price, $2.75.

This is a very practical and easily readable little book that is well recommended for those caring for patients suffering the results of cerebrovascular accidents. It should prove a great help to the families caring for these victims. W.S.

Medicine for the Layman. By Paul Kühne, Pp. 452, illustrated. New York: Robert M. McBride Co., Inc., 1959.

This layman's guide in health matters, by a Berlin physician, has been translated from the German for English readers. The book's jacket calls it, "A Guide to the Intelligent Use of your Doctor." It provides an elementary review of broad scope, supplemented by advice on home remedies and simple nursing procedures. Though readable, more comprehensive works of this type are available to American readers. Pen and ink drawings amplify the text of this handbook. F.R.

Nebraska Symposium on Motivation, 1959. Edited by Marshall R. Jones, University of Nebraska. Pp. 243; 33 ills. Lincoln: University of Nebraska Press, 1959. Price: Paper, $3.00; cloth, $4.25.

This annual contribution to the study of motivation continues on the same high level as in the past. Ranging from the developmental and comparative frames of reference through the anthropological, the current symposium presents a wealth of experimental data and theoretical comment which makes it a must for the serious student of motivation. H.N.

Las Proteinas y los Electrolitos Sanguineos en la Alergia Respiratoria. By Dr. Jorge Raul Vaccarezza. Pp. 61; 5 ills. Buenos Aires: Lopez & Etchegoyen, 1959.

First Report on the World Health Situation, 1954–1956. World Health Organization Official Records, No. 94. Pp. 392; 11 ills. Geneva: World Health Organization, 1959. Price, $3.25.

This new publication by the World Health Organization is an important contribution and one of much practical value. It consists of reports on the health situation of 157 countries and territories throughout the world during the period 1954-1956. The first hundred pages deal with a general survey including chapters on climatic, environmental and other influences affecting the health of peoples, the means of assessing the state of the public health, the administration of health services; institutions and health establishments, education and training. The several country reports give background material on such things as climate, population, economy and health administration, providing a meaningful context for the local health and disease problems. R.K.

The British Encyclopaedia of Medical Practice. Medical Progress, 1959. Edited by The Lord Cohen of Birkenhead, P.R.S.H., M.D., D.Sc., LL.D., F.R.C.P., F.R.C.P.I., F.A.C.P., F.D.S.R.C.S., F.F.R., F.R.I.C., F.S.A., Professor of Medicine, University of Liverpool. Pp. 340. London: Butterworth & Co., Ltd., 1959.

Water Supply for Rural Areas and Small Communities. WHO Monograph Series No. 42. By Edmund G. Wagner and J.

N. LANOIX. Pp. 337; 85 ills. Geneva: World Health Organization, 1959 (Columbia University Press, New York, U.S. distributor). Price, $6.75.

THIS new monograph in the series produced by the World Health Organization deals with the practical solutions of the problem of water supply for rural areas and small communities. The material is arranged in a section on development of a program, the installation of various types of systems and their management. There are numerous excellent illustrations.

R.K.

Annales Universitatis Mariae Curie-Sklodowska. Bibliografia, 1946–1958. Pp. 128. Lublin, Poland: Universitatis Mariae Curie-Sklodowska, 1959.

Methods of Radiochemical Analysis. Report of a Joint WHO/FAO Expert Committee. WHO Technical Report Series, No. 173. Pp. 116; 10 ills. Geneva: World Health Organization, 1959. Price, $1.00.

Joint FAO/WHO Expert Committee on Milk Hygiene. First Report. WHO Technical Report Series No. 124. Pp. 54. Geneva: World Health Organization, 1957. Price, $.60.

THIS report is a concise statement of the principles of hygiene in milk production, processing and distribution, and of legislation to achieve proper milk hygiene and official supervision of milk and milk products. It is available also in French and Spanish and furnishes valuable guide lines in the development of a sound program of milk hygiene.

R.K.

Causation of Cancer. British Medical Bulletin, May, 1958. Pp. 123; illustrated. London: Medical Department of the British Council, 1958. Price, $4.00.

As a memorial to Sir Ernest Kennaway (1881-1958) who had so greatly contributed to the growth of research in the subject, this number of the British Medical Bulletin is devoted to 21 papers on various aspects of the causation of cancer, including Sir Ernest's last paper (with A. J. Lindsey) on Exogenous Factors in Lung Cancer.

R.K.

Antibiotics in Medicine. British Medical Bulletin, January, 1960. Pp. 88; 10 ills. London: Medical Department of the British Council, 1960. Price, $3.25.

THIS number of the British Medical Bulletin is devoted to 16 papers by 20 distinguished British pharmacologists, pathologists, clinicians, surgeons and microbiologists on various aspects of the rapidly developing field of antibiotic therapy, including Chemistry and Classification of Antibiotics, The Nature of Their Selective Toxicity, Drug Resistance, The Principles of Therapeutic Use, The Laboratory Control of Antibiotic Therapy, The Rationale and Management of Combined Therapy, The Pharmacology of Antibiotics, Their Preventive Use in Medicine and Surgery, The Dangers of Antibiotic Treatment, The Chemistry of Tuberculosis and of Bacterial Endocarditis, The Laboratory Uses of Antibiotics and the Search for New Antibiotics.

R.K.

Communicable Diseases in Schools: A Survey of Existing Legislation. Pp. 66. Geneva: World Health Organization, 1959. Price, $.70.

A summary of the isolation and quarantine regulations and procedures as applied in various countries with regard to attendance at school by patients and their contacts.

R.K.

Immunological and Haematological Surveys. Pp. 35. Geneva: World Health Organization, 1959. Price, $.30.

THIS is the report of a study group on immunological and hematological surveys. It summarizes the manner in which serological surveys may be carried out to provide information on the distribution of certain infectious agents, the immunity status of populations, and certain biochemical substances of importance in nutrition and various chronic diseases. Animal as well as human blood can supply much useful information.

R.K.

A Digest of State Air Pollution Laws. Public Health Service Publication No. 711. BY SAMUEL M. ROGERS AND SIDNEY EDELMAN. Pp. 117. Washington: Superintendent of Documents, U.S. Government Printing Office, 1959. Price, $.75.

MEMBERS of health departments will be interested in this digest of State air pollution laws now in force and will find it helpful in planning their own programs.

R.K.

Effect of Small Doses of Alcohol on a Skill Resembling Driving. BY G. C. DREW, W. P. COLQUHOUN AND HAZEL A. LONG, affiliated with the Medical Research Council in Great Britain. Pp. 108; 42 ills. London: Medical Research Council, Memorandum #38, Her Majesty's Stationery Office, 1959. Price, 7s, 6d.

THIS manuscript is a brief report of what would appear to be a very carefully done study on the effect of small doses of alcohol on a skill resembling driving. Procedure was very well done and would appear to be a rather complete and thorough study of the problem on a selected number of individuals.

The appendix is quite complete and it is in the appendix that a comparison between evaluation of urine and breath analysis and blood alcohol contents are compared and different means of measuring these have been devised as well as a comparison in relationship to the dose level and the body weight of the individual. R.T.

A Practical Guide to General Surgical Management. By Julian A. Sterling, M.D., affiliated with Albert Einstein Medical Center, Philadelphia. Pp. 67. New York: Vantage Press, Inc., 1959. Price, $3.00.

This book is primarily a guide to the intern and rather clearly elucidates practical and significant points in the care of surgical patients, both before and after surgery. This might well serve as an intern's guide for any institution not having one of their own. R.T.

A Glimpse of Life in the World to Come. By G. Canby Robinson, M.D. Pp. 85; 1 ill. New York: Vantage Press, Inc., 1959. Price, $2.75.

A prominent physician relates some spiritualistic experiences of his wife's family during a 2-year period in the early 1930's. R.K.

American Handbook of Psychiatry. Edited by Silvano Arieti, M.D., Clinical Associate Professor of Psychiatry, State University College of Medicine at New York City. Pp. 2090 (two volumes); illustrated. New York: Basic Books Inc., 1959. Price, $25.00.

Dr. Arieti states: "This work represents a serious effort on the part of 111 authors to present the development, concepts, trends, techniques, problems and prospects of psychiatry today, in a form useful for both the expert and the beginner, in which every leading school of thought and every major approach is included." The book is offered as being representative of American psychiatry.

The tremendous amount of information contained within the covers of this book will establish it as a valuable reference source. The inclusion of various schools of thought and the presentation of papers that check and balance each other adds breadth on the one hand but on the other hand, makes it read like a series of papers rather than as a book.

The extensive bibliography included by the various authors and the complete subject index enhances the value of the book. M.B.

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